Technological Approaches for Investigating Mechanotransductive Enterogenesis

by

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To my family

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Abstract

Short bowel syndrome (SBS) is a devastating condition characterized by insufficient small bowel length which leads to malnutrition and high rates of mortality. The treatment and management of SBS is difficult, and current approaches suffer from low success rates, lethal complications, and high costs. To improve the quality of care for SBS patients, of which there are approximately 40,000 in the USA, this research investigated technological approaches for a promising and novel treatment approach based on mechanotransductive enterogenesis, a process in which longitudinal small bowel tissue growth is induced by the application of tensile loading. Three enterogenesis device technologies were designed to attach to segments of small bowel tissue and extend, thereby placing the tissue under tension and inducing growth. Each device was used in experimental *in vivo* studies with clinically relevant porcine animal models to advance the knowledge of mechanotransductive enterogenesis for correcting SBS. The Curved Hydraulic Device was used to induce high expansion bowel lengthening, establishing the clinical feasibility of the mechanotransduction-based approach. The Instrumented Shape Memory Alloy Driven Ratchet, designed with the new Reset View Design Methodology and rack/pawl force interaction model, was used to develop the treatment approach by determining the limit of safely applied bowel tension, comparing the effect of applying different tissue expansion profiles on tissue growth, and exploring the limits of the maximum tissue expansion rate. Lessons from these studies led to the Reciprocating Linear Hydraulic Device, which was used to successfully demonstrate the viability of a high-expansion cyclical bowel lengthening approach by lengthening a segment of small bowel tissue by more than the device stroke. The success of this approach depended on the development of a clinically relevant tissue attachment approach, the Dilating Fenestrated Mesh, which was developed through the *in vivo* evaluation of a broad range of attachment approaches that characterized their attachment performance, ease of implantation/removal, and risk of causing surgical complications. This dissertation has made important contributions toward the advancement of this vital new treatment approach for SBS through the innovation of enterogenesis device technologies, the development of experimental methodologies, and an understanding of the mechanical device/tissue interaction.

CHAPTER ONE. INTRODUCTION

Short bowel syndrome is a serious medical condition characterized by insufficient small bowel length which leads to malabsorption, poor quality of life, and high rates of mortality. The treatment and management of short bowel syndrome is difficult, and current approaches suffer from low rates of success, lethal complications, and high costs. The clinical feasibility of lengthening small bowel by inducing its growth through the application of tensile load (mechanotransductive[1] enterogenesis[2]) was hinted at in studies with rat and rabbit animal models, but there is a large gap between these studies and the clinical realization of the approach. To improve the quality of care of short bowel syndrome patients, the goal of this dissertation is to narrow this gap by exploring technological approaches for a promising and novel treatment method of short bowel syndrome based on mechanotransductive enterogenesis in clinically relevant porcine animal models. The objectives include establishing the clinical feasibility of the mechanotransductive approach, developing the treatment approach by exploring displacement and tension-based tissue expansion strategies, investigating clinically relevant small bowel attachment approaches, and developing clinically relevant enterogenesis device technologies and tissue lengthening approaches. To explore these objectives, a series of novel enterogenesis devices were designed, fabricated, and used to enable *in vivo*[3] experimental studies of mechanotransductive enterogenesis in porcine animal models. Attachment approaches for transferring load from enterogenesis devices to bowel tissue were investigated in a series of acute and longer-term *in vivo* studies. This dissertation makes important contributions to the disciplines of surgery and engineering, which together constitute the

[1] Mechanotransductive: Relating to the process through which mechanical stimuli elicit a biochemical response in living cells
[2] Enterogenesis: Growth of bowel tissue
[3] *In vivo*: Occurring within live animal

complete foundation supporting the design and usage of enterogenesis technologies for correcting short bowel syndrome.

1.1. Short Bowel Syndrome

Short bowel syndrome (SBS), or short gut syndrome, is a devastating medical condition characterized by the malabsorptive state of a patients, primarily infants and children, who have undergone massive small bowel resection[4] to treat intestinal pathologies. Although less common, SBS may also be caused by congenital[5] small bowel atresia[6]. The length of small bowel removed that results in malabsorption varies greatly from patient to patient as a result of differences in age, the part of small bowel resected, and the health of other organs in the digestive system [1]. Thus, definitions of SBS vary greatly in the literature. Rickham, who coined the name "short bowel syndrome" in 1967, stated that patients having less than 30% of small intestine remaining (75cm for neonates and 150-200 cm for adults) would develop SBS [2]. Recent definitions state that SBS develops when less than 200 cm of small intestine remains following resection in adults [3,4], and/or the long-term requirement of Parenteral Nutrition (PN) following bowel resection [5,6]. A consensus definition has been proposed to aid patient diagnosis and treatment [7]: *"Short-bowel syndrome – intestinal failure results from surgical resection, congenital defect or disease-associated loss of absorption and is characterized by the inability to maintain protein-energy, fluid, electrolyte or micronutrient balance when on a conventionally accepted, normal diet."*

1.1.1. Etiology

The etiology, or cause, of massive small bowel resection leading to SBS varies between infants and adults. The small bowel is fed blood almost entirely by the superior mesenteric artery, which connects to the small bowel via the mesentery, a thin membrane suspending blood vessels (Figure 1.1). Not surprisingly then, the health of the small bowel is strongly coupled to that of the superior mesenteric artery and its companion vein, which drains blood away from the small bowel. Injury to either vessel related to trauma and or abnormal intestinal pathologies may lead to small bowel resection and subsequent SBS. Among infants, necrotizing enterocolitis, the death of small bowel tissue, and midgut volvulus, the abnormal looping of small bowel upon itself, are leading

[4] Resection: Surgical removal
[5] Congenital: Present at or before birth
[6] Atresia: Absence or closure of orifice or bodily passage

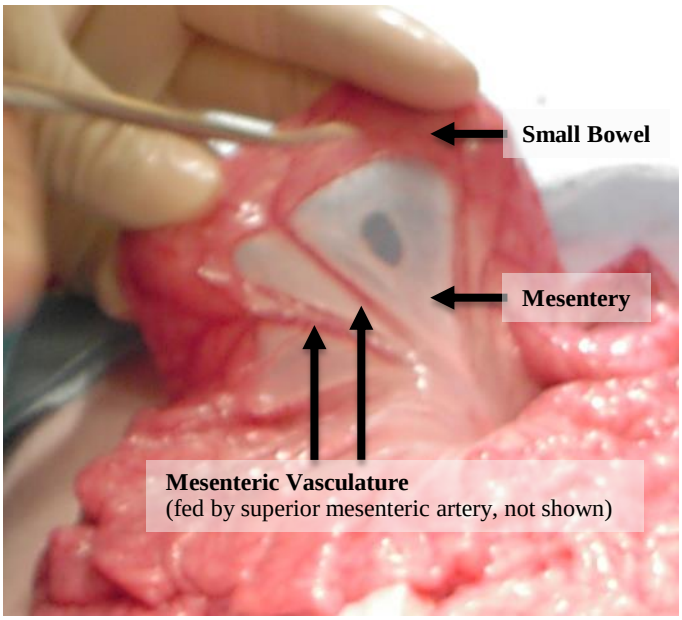

Figure 1.1. Basic Gross Anatomy of Small Bowel and Supporting Vasculature. The small bowel consists of three major segments: the duodenum, which connects to the stomach, the jejunum, the middle portion, and the ileum, which connects to the large bowel through the ileocecal valve. The small bowel is supported by vasculature embedded in the mesentery, the thin membrane connecting the small bowel to the superior mesentery artery and its companion vein.

causes of the requirement for massive resection leading to SBS [1]. In both pathologies, a reduction of blood to the small bowel tissue plays an important role in the deterioration of its health and functionality. Intestinal atresia, a condition where an underdeveloped portion of small bowel causes obstruction, requires resection to restore the flow of enteric contents. Gastroschisis, a prenatal condition where small bowel exits the body through a defect in the umbilical cord, is also a cause of significant bowel resection. Additional causes in infant populations include genetically inherited motility disorders such as total aganglionosis[7], chronic intestinal pseudo-obstruction[8], and congenital short bowel [8]. Among adults, common indications for massive bowel resection are radiation enteritis[9], cancer, mesenteric vascular disease, and severe Crohn's disease[10] [1,6]. Tables 1.1 and 1.2 document the conditions causing massive bowel resection in adult and pediatric

[7] Total aganglionosis: Absence of ganglion cells in entire colon that causes inability of tissue to relax, creating an obstruction
[8] Intestinal pseudo-obstruction: A condition characterized by constipation, colicky pain, and vomiting, but without evidence of organic obstruction apparent at laparotomy
[9] Enteritis: Inflammation of small bowel
[10] Crohn's disease: A type of inflammatory bowel tissue that can affect any portion of the GI tract

Table 1.1. Conditions leading to massive resection in pediatric patients.
Table adapted from [6]. The leading causes of massive resection in pediatric populations are necrotizing enterocolitis and midgut volvulus.

Condition resulting in massive resection, pediatric patients.

Condition	No.	%
Necrotizing enterocolitis	37	33
Midgut volvulus	36	32
Intestinal atresia	23	21
Other benign disease	16	14
Total	112	100

Table 1.2. Conditions leading to massive resection in adult patients.
Table adapted from [6]. The leading causes of massive resection in are populations are cancer secondary to irradiation and mesenteric vascular disease.

Condition resulting in massive resection, adult patients.

Condition	No.	%
Irradiation/cancer	17	35
Mesenteric vascular disease	10	21
Crohn's disease	5	10
Other benign disease	16	33
Total	48	100

patients, respectively, from a single-institution retrospective review [6]. However, the relative rates of etiologies are typical and highlight the contrast between causes in infants and adults.

1.1.2. Effects of Short Bowel Syndrome

For the estimated 40,000 [9] patients in the United States with SBS, the symptoms of the condition are devastating. Ingested food is malabsorbed, leading to diarrhea and the subsequent excessive loss of nutrients, fluids, and electrolytes. In infants, the lack of nutrition results in an inability to thrive and develop. When left untreated, the development of symptoms similar to chronic dehydration may also occur. Furthermore, massively dilated portions of small bowel are common in SBS patients, leading to a motility disorder where the flow rate of enteral contents is reduced. The reduction of enteral content flow begins a cascade of events: bacterial overgrowth, translocation of bacteria and toxins, recurrent sepsis[11], cholestasis[12], and eventually liver failure. As a result, SBS is a highly lethal condition, particularly for infants and children, with mortality rates exceeding 30% [1,4,5,7,10–13]. The cost of care is high, with the average first year single patient total exceeding half of a million USD and subsequent years steadily costing 250,000 to 300,000 USD/year on average [14]. Therefore, the burden of SBS is severe both financially and medically.

[11] Sepsis: A bacterial infection in the bloodstream or body tissues.
[12] Cholestasis: A condition caused by rapidly developing or long-term interruption in the excretion of bile (a digestive fluid that helps the body process fat).

1.1.3. Treatment and Management Methods

The approach to the management and treatment of SBS can vary greatly from patient to patient, and is dependent on many factors including the presence of the colon, the presence of the ileocecal valve[13], the health of other organs in the digestive system, patient age, the extent of remnant bowel dilation, and importantly, the length and location of remnant bowel. Although the approach to treatment and indications for surgery will vary from institution to institution, Figure 1.2 illustrates a typical treatment plan, which is simplified to account mainly for two factors: extent of bowel dilation and remnant small bowel length. Non-surgical approaches to the treatment of SBS include administering Total Parenteral Nutrition to sustain patients while the bowel undertakes adaptive processes to increase enteral nutrient absorption, and the use of growth hormones to hasten the adaptation. If patients cannot wean from Total Parenteral Nutrition,

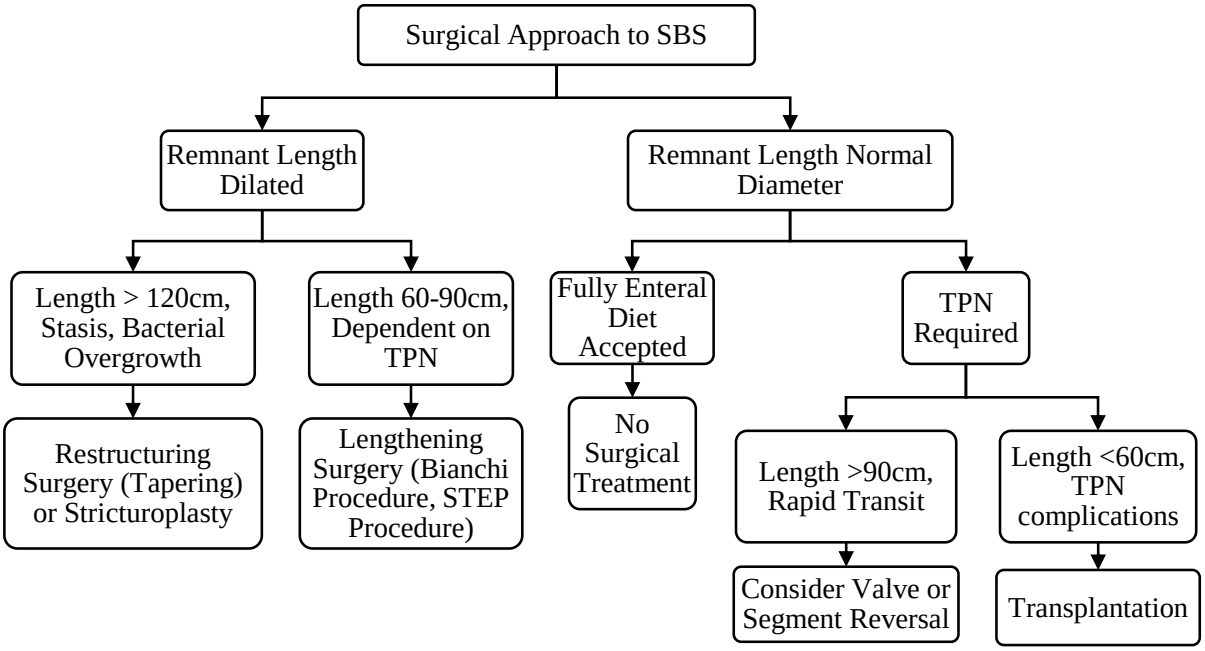

Figure 1.2. Conventional Approach to Surgical Treatment.
Figure adapted from [6]. Based the length of remnant small bowel following resection and the extent of remnant bowel dilation, different approaches to treating SBS are commonly indicated. When the segment is sufficient in length but dilated, surgical tapering to reduce the dilation is considered. If bowel dilation is proximal to a stricture, a small narrowing of the bowel, stricturoplasty may also be considered. In the best case, the remnant bowel is not dilated and a fully enteral diet is accepted. Thus, no surgical treatment is necessary. Regardless of the dilation extent, if Total Parenteral Nutrition (TPN) is required long-term and leads to complications, surgical bowel lengthening procedures may be considered such as the Bianchi Procedure, Serial Transverse Enteroplasty (STEP), and transplants.

[13] Ileocecal valve: Valve at junction separating the small intestine from the large intestine

surgical options are considered to restructure and lengthen bowel, and bowel transplant is also considered.

1.1.3.1. Non-Surgical Approach

The mainstay of treatment for SBS is Total Parenteral Nutrition (TPN), a high caloric and nutrient rich solution that is feed intravenously into patients [15]. TPN manages the symptoms of SBS stemming from the malabsorption of nutrients, but does not treat the cause of SBS. Due to the potentially lethal complications and high costs associated with long-term reliance on TPN, ideally patients on TPN are able to gradually wean to a normal diet. From Medicare data, the yearly cost of TPN exceeds 150,000 USD, and that figure does not include additional costs due to frequent hospitalization, medical equipment, and nursing care [16]. High calorie TPN solutions required by neonates and infants may cause a reduction of bile flow, known as Parenteral Nutrition Associated Cholestasis (PNAC), which can lead to cholestatic liver injury, irreversible cirrhosis[14], and eventually death. Furthermore, long-term reliance on TPN may also lead to recurrent sepsis and thrombosis[15] from bacterial contamination of the feeding catheter.

The acceptance and absorption of EN depends on the extent to which the remnant small bowel adapts following a major resection. The adaptation process is characterized by an increase of villus height and crypt depth[16], mucosal hyperplasia[17], and bowel dilation [12,17], all of which effectively increase the absorptive area in an attempt to compensate for a loss of length. However, bowel dilation can negatively affect motility, potentially resulting in bacterial overgrowth, and require bowel restructuring surgeries. Factors that affect small bowel adaptation include the length and location of the remnant bowel, age, underlying cause of requirement for massive resection, health of other organs in the digestive system, and the presence of the ileocecal junction [6]. To hasten the adaptive process, the use of growth hormones, growth factors, and nutrients have been explored with mixed results [4,18–22]. Although an increase in absorption of nutrients has been clinically observed [18,21], a major problem associated with this approach has been a reversal of the absorptive gains at the end of the treatment period [22].

[14] Cirrhosis: Cirrhosis is scarring of the liver and poor liver function. It is the final phase of chronic liver disease
[15] Thrombosis: The formation of blood clots
[16] Villi and Crypts: The features of the innermost layer of small bowel (mucosa). Villi are outward projections of the mucosa, while crypts are inward
[17] Mucosal hyperplasia: An increase in the number of cells of the mucosa

Both TPN and natural bowel adaptation play an important role following major small bowel resection, but not all patients wean from TPN. It is possible to achieve long-term success with TPN in cases where small bowel adaption does not fully wean patients to EN, but the high complication rate, poor quality of life, and expense of TPN has encouraged the development of surgical options [23].

1.1.3.2. Surgical Approach

In cases where lengthening of the bowel is not necessary but the transit of enteral contents is abnormally slow or fast, surgical restructuring techniques are considered. When the flow of enteral content is abnormally slow, bacterial overgrowth can occur, whereas abnormally fast enteral content flow can lead to malabsorption. Dilated bowel segments slow the flow of enteral contents, and may be surgically tapered, as shown in Figure 1.3. A bowel stricture also slows the flow of enteral content and causes proximal[18] bowel dilation, resulting in the consideration of a stricturoplasty (Figure 1.3). In cases where the transit of enteral contents is too rapid, the introduction of a valve or a reversed segment of bowel may be considered.

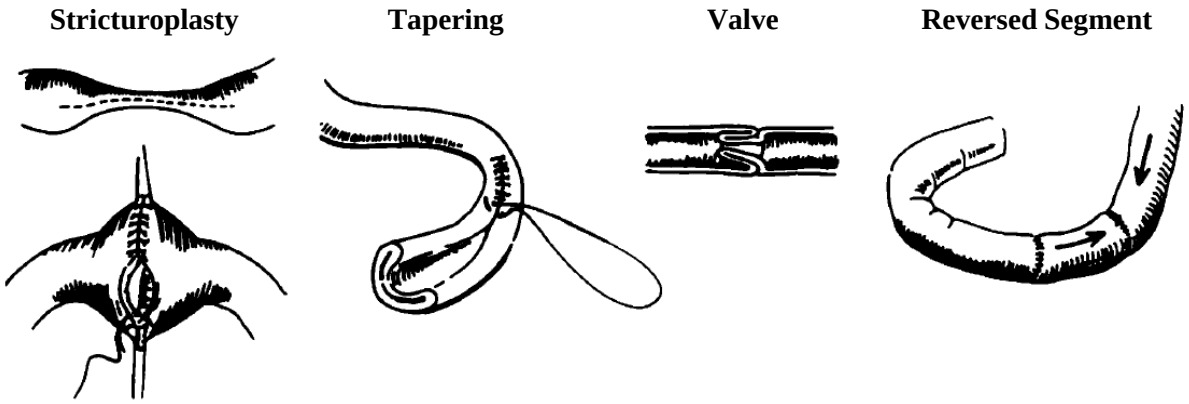

Figure 1.3. Surgical Structuring Approaches.
Image taken from [6]. Surgical techniques for increasing or reducing the rate of enteral content transit through the small bowel are shown. In cases where the transit of enteral content is slow, bacterial overgrowth can occur and lead to sepsis. To increase the rate, strictures in the bowel are removed by stricturoplasty and dilated portions of bowel are tapered. In cases where the flow is too rapid, the bowel cannot properly absorb nutrients. To decrease the rate, valves can be surgically implement as well as reversed segments of bowel. Reversing a segment of bowel works because naturally occurring peristalsis in the reversed segment will work to move enteral content opposite the normal flow.

[18] Proximal: Upstream

After significant small bowel resection, naturally adaptive processes may not completely wean SBS patients from TPN. For these cases, two surgical lengthening techniques, known as the Bianchi Procedure and the Serial Transverse Enteroplasty (STEP), may be considered to lengthen the small bowel and improve its absorptive capacity. Additionally, bowel transplantation is another surgical bowel lengthening approach. For the Bianchi and STEP procedures, a dilated portion of bowel is required to be tapered and lengthened. The surface area for nutrient absorption is not increased by either technique initially. However, both surgeries significantly reduce the inner diameter of the bowel, which then adapts by increasing it inner diameter following the surgery and leading to a greater area of absorption. Additionally, tapering dilated bowel segments in this manner has the additional benefit of decreasing the risk of bacterial overgrowth secondary to the slow transit of enteral contents.

1.1.3.2.1. Bianchi Procedure

The first surgical small bowel lengthening technique was developed by Bianchi and results with porcine models were reported in 1980 [24]. The Bianchi procedure, also known as Longitudinal Intestinal Lengthening and Tailoring (LILT), is shown in Figure 1.4 as a five step procedure consisting of A, splitting the mesentery lengthwise along the bowel, B, further separating mesentery from bowel to make room for a staple line, C, applying a line of staples, D, separating the two new segments of bowel, and E, anastomosing[19] the ends of the two new segments such that the direction of peristalsis is not reversed. The procedure doubles the length of the typically dilated bowel that it is performed on while simultaneously reducing the diameter, a result that quickens the flow of enteral contents and prevents bacterial overgrowth.

The clinical application of the Bianchi procedure has been associated with serious complications and the need for further surgical lengthening procedures and bowel transplant. In a 20-year single institution (St. Mary's Hospital, Manchester, UK) study consisting of 20 patients, an increase in nutrient absorption was observed, but at a mean follow up period of 6.4 years, the mortality rate of the patients was 55%. The most prominent complication was hepatic[20] failure (10 out of the 11 patients that died). Of the 9 surviving patients, 7 weaned completely from TPN [25,26]. Another more recent retrospective study of a 20-year single institution experience

[19] Anastomosis: A surgically made connection between tissues, usually between tubular structures.
[20] Hepatic: Relating to the liver

(Children's Hospital of Pittsburgh) was reported with 19 patients, 7 of which weaned from TPN, 9 of which required bowel transplants, and 3 of which were still on TPN [27]. In another single institution (Mannheim University Hospital, Heidelberg University, Germany) series, 49 patients from 1982 to 2004 underwent a modified (no stapler used, manual suture lines) Bianchi procedure [28]. Of the 49 patients, 19 weaned off of TPN, 5 were still on TPN at follow up, 16 patients were not followed up, and 9 died from complications including liver failure (n = 4) and sepsis (n = 3). The most prominent long-term complication reported was bowel re-dilation leading to reduced motility, stasis, bacterial overgrowth and malabsorption.

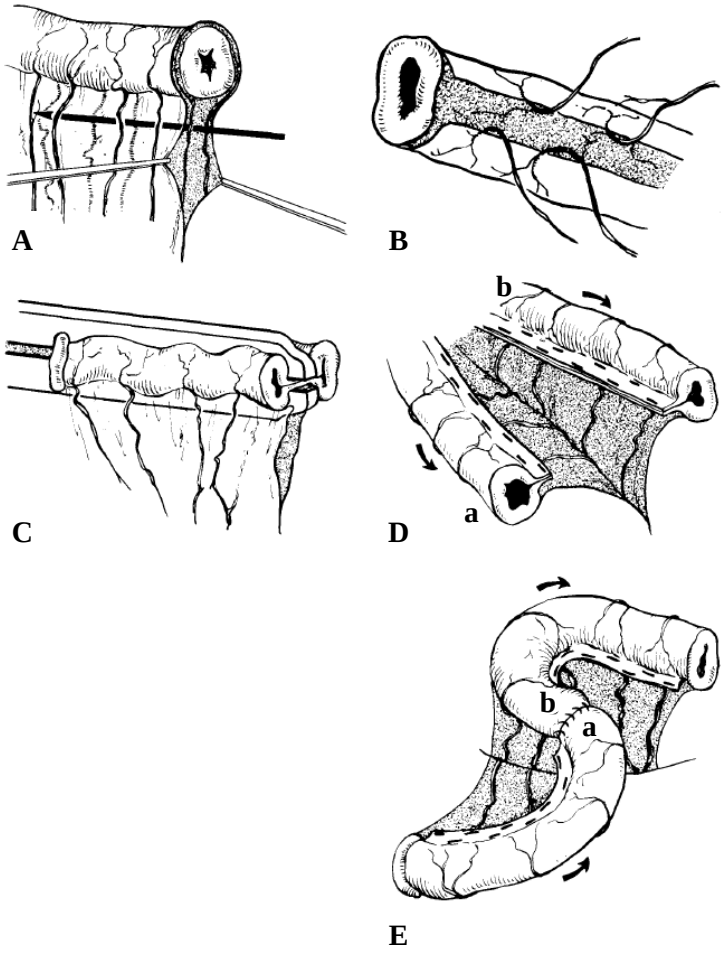

Figure 1.4. The Bianchi Procedure.
Taken from [24]. The Bianchi Procedure is illustrated in five steps. A, the mesentery is split into two halves and disconnected from the mesenteric side of the bowel (B). C, a staple line is introduced into the bowel such that neither half of the mesentery is cut, creating to segment of bowel from one (D). Lastly, the two segments of small bowel are reconnected, such that the peristaltic action of both segments does not opposed the natural flow of the GI tract.

1.1.3.2.2. Serial Transverse Enteroplasty

The Serial Transverse Enteroplasty Procedure, or STEP, was developed by Kim *et al.* [29] and results with 6 porcine models were reported in 2003. The STEP procedure is sometimes preferred to the Bianchi procedure, because it is easier to perform and doesn't require anastomoses [30]. However, the Bianchi procedure cannot be performed to a bowel segment where a STEP procedure was previously performed, while a STEP procedure can follow a Bianchi procedure. Thus, the Bianchi procedure is sometimes preferred as the first bowel restructuring technique. The STEP procedure consists of creating a zigzag path by creating staple lines on alternating sides of the small bowel, as shown in Figure 1.5. In the initial study, the 6 porcine models gained weight, had no bowel obstruction, no dilation at six weeks post operation, and on average, the STEP segment of bowel was lengthened from 49.2 to 82.8 cm. Like the Bianchi procedure, the STEP procedure narrows the diameter of the small bowel, helping to prevent stasis and bacterial overgrowth.

The first clinical case report [31] was a two-year-old boy with a prior Bianchi procedure at the Children's Hospital in Boston, MA. The STEP procedure successfully lengthened 83 cm of

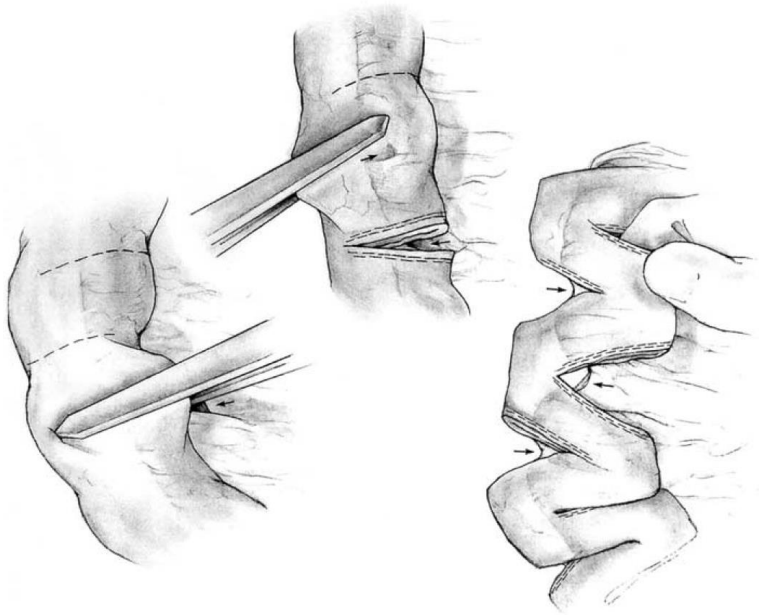

Figure 1.5. Serial Transverse Enteroplasty Procedure Schematic.
Image taken from [29].The Serial Transverse Enteroplasty (STEP) lengthening segments of dilated small bowel by introducing zigzagging staple lines into the small bowel which subsequently straighten out. For each staple line, a small mesenteric defect is created to position the stapling tool.

previously dilated bowel to 147 cm, making the entire length of the small bowel 200 cm. The patient tolerated the procedure well and had a significant increase in absorptive capacity. Recent reports of STEP procedures at the Children's Hospital in Boston documented the outcome of 16 surgeries from February 2002 to February 2008 [32,33]. Of the 16 patients, 6 have weaned completely from TPN, 2 patients required transplants, and complications included catheter-related bacteria (n = 5), GI bleeding (n = 1), and bowel obstruction (n = 1). An average length increase of the STEP segment of 91% and no deaths were reported.

The outcome of 14 patients who underwent the STEP procedure from May 2003 to May 2006 at the Hospital for Sick Children, Toronto, CA is reported in a retrospective study [30]. Of the 14 patients, 8 were followed up at more than 1 year post operation, 7 of which were able to wean off TPN. Complications included GI bleeding (n = 1), staple line leakage (n = 2), and 3 patients died from liver failure (n = 2) and a combination of sepsis and heart failure (n = 1). In addition to the STEP procedure, 2 patients required liver/bowel transplants. An average increase of the STEP segment length of 94% was reported.

Another single-institution retrospective chart review of 119 patients seen from January 1995 to December 2009 at the University of Michigan reported the results of 14 patients receiving the Bianchi procedure (n = 5) and the STEP procedure (n = 9). Within this cohort, two patients who received the STEP procedure required an additional STEP procedure to eliminate bowel re-dilation that was causing bacterial overgrowth and malabsorption [34]. Two patients who received the Bianchi procedure required a subsequent STEP procedure. Of the 9 patients who underwent the STEP procedure, 3 patients were able to wean completely off of TPN, an additional 3 patients continued to decrease their requirement for TPN for greater than one year post operation, and there was one death from the combination of a bleeding stress ulcer and parenteral nutrition associated liver disease. Complications associated with the STEP procedure included bowel re-dilation, bacterial overgrowth, GI bleeding, the requirement for reoperation, adhesive small bowel obstruction, and strictures. Of the eight patients who experienced bowel re-dilation, 7 required re-operation and only one patient weaned off of TPN, whereas no patient in the un-dilated group required an additional operation.

An International STEP Data Registry was formed to acquire sufficient data for facilitating analysis [35]. From September 2004 to April 2006, 38 patients from 19 centers and 3 countries

have enrolled in the registry. Reported complications include leakage along staple lines (n = 2), bacterial overgrowth (n = 2), abscesses (n = 3), the necessity of reoperation (n = 3), and death (n = 3). The average percentage of enteral nutrition accepted increased from 31% to 67%, and the average length of the STEP segment increased from 68 cm to 115 cm.

While both procedures increase the length of the small bowel and facilitate weaning from parenteral nutrition, many of the complications associated with the Bianchi and STEP procedures are not uncommon and necessitate the requirement for further surgical intervention. In particular, bowel re-dilation and enteral content leakage are common complications that can lead to a cascading set of worsening complications. Therefore, other treatment modalities, such as bowel transplant, are sometimes preferred to surgical lengthening with either the Bianchi or STEP procedures.

1.1.3.2.3. Bowel Transplant

Bowel transplants may be considered for patients who have undergone extreme bowel resection, aren't weaning from TPN, or do not have the dilated lengths of small bowel that make surgical lengthening practical. The motivation for transplants stem from the technical and immunologic problems associated with TPN, which lead to high costs and mortality rates. If performed early, bowel transplant may prevent parenteral nutrition associated liver disease [6].

Bowel transplants are surgically challenging, and compared to other organ transplants, have lower survival rates [36]. Furthermore, patients require long-term immunosuppressive medication, and the surgery can cost in excess of 210,000 USD [16]. Although the short-term patient and graft survival rates have seen improvement, the most recent results on an estimated 95% of bowel transplants performed from 1999 to 2009 have a 50% patient mortality rate at five years post operation [37].

1.1.4. Treatment Outcomes

Despite the improvements made in the last decade with the administration of TPN, new surgical lengthening and tapering options such as STEP, and improved short-term patient/graft survival rates with transplants, SBS remains one of the most lethal conditions for infants and children [38]. TPN is costly, and long-term reliance on TPN continues to be associated with lethal complications. Surgical lengthening techniques such as the Bianchi Procedure and STEP lengthen

bowel and can improve bowel motility short-term, but both procedures are invasive and suffer from complications including bowel re-dilation and leakage along the lengthy staple lines. Bowel transplants can dramatically increase the length of small bowel in patients, but continue to suffer from dismal long-term graft rejection rates. The severity of complications associated with the traditional treatment methods has led to high rates of mortality and morbidity. Overall rates of mortality vary greatly in literature, but large intestinal failure centers have recently reported mortality rates exceeding approximately 30 percent [1,4,7,13–15] with some reaching as high as 37.5% [5,16]. To improve on these outcomes, a new approach to lengthening small bowel based on mechanotransduction has been evaluated in experimental studies with small animal models.

1.2. Mechanotransductive Treatment Approach

To improve the survival rate of SBS patients, a new approach for treating patients based on mechanotransductive enterogenesis, the induction of small bowel tissue growth by the application of mechanical loading, appears very promising. Mechanotransduction is the process through which a mechanical stimulus excites a biochemical response at the cellular level. All biological tissues respond to shear and or normal forces by growing, changing compliance, and a wide range of other physiological changes [39]. The migration, proliferation, differentiation, and apoptosis of living mechanosensitive cells are modulated by force [39], the cumulative effect of which can profoundly affect the development and function of organs and tissues. However, the mechanisms by which the transduction occurs within living cells are not fully understood [40–42]. Examples of mechanotransduction in the regulation of normal processes are widespread and diverse, as a result of the universal nature of cellular mechanosensitivity.

Due to the vast number of possible congenital and acquired bone, tooth and soft tissue deformities and injuries, there are a plethora of medical treatments based on mechanotransduction where the correction of these conditions is achieved. Bone growth, or osteogenesis, is achieved by the application of tensile, or distractive, loading on the fibrocartilage callus that forms in the gap created between the segments a broken bone [43]. Distraction osteogenesis is used both in pediatric and adult populations for correcting mismatched leg lengths, congenital or acquired bone malformation, and for growing bone to replace segments surgically removed because of tumors. Favorable outcomes are reported for numerous distraction osteogenesis based treatments including

cranial vault expansion [44], mandibular distraction [45–47], brachymetatarsia[21] [48], and failed pollicization[22] [49]. Like bone, the ability to induce the growth of soft tissues by gradual expansion and loading provides a wide range of medical treatments [50]. Following a mastectomy, reconstruction of the breast(s) may be achieved by the gradual expansion of a bladder implanted within a subpectoral pocket [51,52]. Many congenital conditions are treated by the load induced growth of soft tissues such as the management of giant omphaloceles[23] and melanocytic naevi[24] [53,54], abdominal wall defects [55], hypospadism[25] [56], anophthalmos[26] [57], and long-gap esophageal atresia[27] [58,59]. The breadth of soft tissues that may be grown by the application of external force suggests the potential for the tension-induced growth of small bowel in the treatment of short bowel syndrome.

1.2.1. Prior Mechanotransduction Based Enterogenesis Research

There has been very promising yet limited research studies conducted on the process of tension-induced enterogenesis. The underlying process of mechanotransduction, defined as the biological response of a cell to a mechanical stimulus, has resulted in the growth of small bowel segments as demonstrated in previous *in vivo* studies with rat [60–67] and rabbit [68] animal models[28], but not in larger more clinically relevant animal models such as pigs. In these experiments, three enterogenesis devices were used to apply tensile load: the Internal Screw, the External Screw, and the Intraluminal Spring.

The Internal Screw Device [68] (Figure 1.6) is an extraluminal device and is unique in that it was designed for tensioning continuous, or non-isolated, segments of rabbit small bowel. The device is composed of two perforated semicircular tissue couplers that attach to the antimesenteric side of the small bowel with sutures, and two lead screws that drive the attachments along the length of the slotted housing. The attachments are initially close to the center of the housing at the start of the implantation period. While implanted, the attachments are separated gradually by

[21] Brachymetatarsia: Condition where one or more metatarsals are abnormally short
[22] Pollicization: Surgical construction of thumb using a finger
[23] Omphalocele: Birth defect where the bowel, liver, or other abdominal organs protrude through a defect in the abdominal wall
[24] Melanocytic naevi: Moles
[25] Hypospadism: Male birth defect where urethral orifice is misplaced along the underside of the penis rather that at the tip of the glans
[26] Anophthalmos: Absence of ocular tissue
[27] Esophageal atresia: Absence or gap of length of esophagus
[28] Animal model: A living non-human animal used to conduct medical experiments for studying human diseases and medical conditions

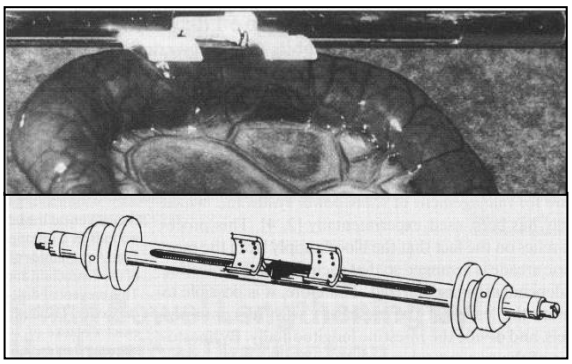

Figure 1.6. Internal Screw Device.
Figure adapted from [68]. The first enterogenesis device was the internal screw, which was device for studying the load-induced growth of small bowel tissue in rabbit models. The device was extraluminal, and attached to the rabbit small bowel with sutured semicircular rings. To apply tensile load, the ring attachments were separated by turning the screw, which extended out of the rabbit abdomen.

turning the screws protruding from the rabbits' abdomen. The tissue couplers displace as the screws are turned because they have threaded holes at their base, through which the screw is placed, and are prevented from rotating by interference from a slot running lengthwise the device.

Designed for rats, the External Screw Device [64] (Figure 1.7) works by feeding a screw through a threaded hole on an externally mounted structure affixed to the animal model's abdomen with sutures. Unlike the internal screw, the external screw applies tension to the blind end of an isolated segment of small intestine that is sutured to an ostomy through which the screw is inserted.

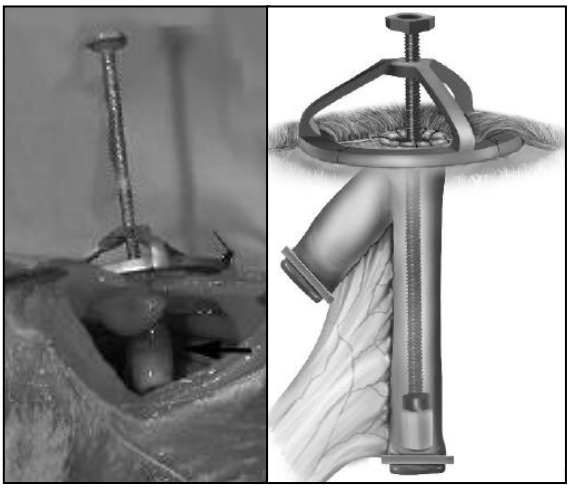

Figure 1.7. External Screw Device.
Figure adapted from [64]. The external screw device was designed for studies with rats. To apply load, the end of the screw abuts a blind-ended segment of isolated small bowel tissue as the screw is turned.

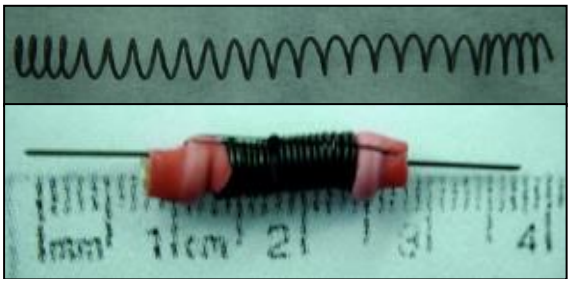

Figure 1.8. Intraluminal Spring.
Figure adapted from [65]. The intraluminal spring was designed for studies with rats. To apply load, the spring is implanted in an isolated segment of small bowel with the spring compressed by a dissolving suture. Once dissolved, the spring abuts the ends of the isolated tissue segment.

While the screw is feed through the external structure and ostomy, the end of the screw abuts a suture line at the end of the small bowel segment, thus applying tension and inducing growth.

Designed for rats, the most recently reported enterogenesis device is a superelastic nickel titanium (NiTi) Intraluminal Spring [65] that is initially held compressed by dissolvable sutures and implanted in an isolated small bowel segment (Figure 1.8). With the NiTi spring, the tensioned segment of bowel is isolated so that the ends of the spring can transfer load to the tissue by end abutment and to prevent bowel obstruction. When the sutures break down, the spring expands and abuts the surgically closed ends of the isolated bowel segment in which it is implanted. This process continues until the spring is fully extended, as determined by tracking its extension with radiographs.

Different tissue evaluation approaches and control segment choices were used in the prior studies with small animal models. In the rabbit study, the Internal Screw Device expanded a segment of bowel that was part of the continuous GI tract and a non-tensioned portion of normal small bowel was used as a control. For the rat studies, which used the External Screw Device and Intraluminal Spring, the lengthened bowel segments were isolated from the continuity of the GI tract and not exposed to enteral nutrition. Therefore, the control segments for the rat studies were similarly isolated and unfed segments of bowel tissue. Although each research group has approached the evaluation of the tissue segments differently, the tissue health analyses listed below were the most common.

1. Morphological Changes

   Morphological features of the distracted small bowel were measured and compared with controls to evaluate changes in the longitudinal and circular muscle layer thickness, serosal thickness, mucosal thickness, villus height and width, and crypt depth. The preservation of these structures' dimensions is a positive indicator of bowel growth and health. Purely stretching bowel would lead to decreased thicknesses of the layers of the bowel and wider villi. Studying the morphological features also reveals the extent of tissue inflammation, tearing within the muscle layers, and mucosal disruption.

2. Enzyme Activity

   Measuring the enzyme activity of small bowel indicates the absorptive capacity of the tissue. Increases of total enzyme activity within the distracted segments is a positive indicator of true bowel growth versus stretching, as merely stretched bowel would maintain or experience a reduction of total enzyme activity. In addition, the reduction of total enzyme activity may be caused by physical disruption of the mucosa.

3. DNA, RNA, and Protein Concentrations

   DNA, RNA, and protein concentrations are measured to evaluate whether or not there is a tissue cellularity difference with control segments. The preservation or increase of tissue cellularity indicates true small bowel growth.

4. Cell Proliferation

   The percentage of proliferating cells was measured to indicate the health of the grown small bowel tissue. Healthy normal bowel mucosa is constantly sloughing off and producing new cells. However, in segments where bowel growth is occurring, the percentage of proliferation cells will be equal to or higher than that of control segments.

1.2.1.1. Experimental Study Growth Results

The growth results of the rabbit and rat studies are summarized in Table 1.3. Using the Internal Screw Device, the mechanotransductive response of small bowel tissue was first demonstrated in healthy (normal bowel length) rabbit models (n = 27) by Printz *et al.* in 1997 [68]. Segments of 1 cm in length were doubled to 2 cm by the application of distractive force over the course of 3 weeks. Using the External Screw Device, Park *et al.* [62] doubled the length of small bowel segments, from 1.5 cm to 3 cm, in healthy rat models (n = 10) during a three week distraction period. Also using the External Screw Device, Safford *et al.* [64] increased the length of small

bowel segments by a factor of 2.5, from 0.76 cm to 1.9 cm, in healthy rat models (n = 50) during a 30 day distraction period. Chang *et al.* [60] sought specifically to evaluate the stability of the distracted segments of small bowel in rats (n = 20) in the absence of distractive forces following bowel tensioning. During a one-week distraction period, small bowel segments were approximately doubled in length from 1.5 cm to 3.1 cm using the External Screw Device. After waiting 3 weeks with the distracted segment under no further applied tension, the distracted small bowel lengths were measured again as 3.2 cm ($p > 0.05$) for rats in the waited group, demonstrating the stability of the grown tissue segments. Using the Intraluminal Spring, Shekherdimian *et al.* [65] increased the length of small bowel segments in rats (n = 5) by a factor of 3.40, from 1.3 cm to 4.4 cm. Stark *et al.* modified that Intraluminal Spring, replacing the dissolving sutures with a dissolvable gel coating to hold the spring compression, and conducted two studies where rat small bowel (n not reported) was expanded by factors of 3.6 in two weeks [66], and 3.3 [67] in 18 days.

Table 1.3. Reported Enterogenesis Results with Current Devices.
Bowel growth results using the Internal Screw Device, External Screw Device and Intraluminal Spring are listed in chronological order. The growth, or expansion, ratio of tissue using the Internal Screw Device and External Screw Device ranged from 2 to 2.5, while the Intraluminal Spring ranged from 3.3 to 3.6.

Device	Animal Model, n	Initial Segment Length (cm)	Final Segment Length (cm)	Net Growth (cm)	Growth Ratio	Author and Citation
Internal Screw	Rabbits n = 27	1	1.99	0.99	1.99	Printz *et al.* [68]
External Screw	Rats n = 10	1.5	3	1.5	2.00	Park *et al.* [62]
External Screw	Rats n = 50	0.76	1.9	1.14	2.50	Safford *et al.* [64]
External Screw	Rats n = 20	1.5	3	1.5	2.00	Chang *et al.* [60]
Intraluminal Spring	Rats n = 5	1.3	4.4	3.1	3.38	Shekherdimian *et al.* [65]
Intraluminal Spring	Rats (n not reported)	1.0	3.6	2.6	3.60	Stark *et al.* [66]
Intraluminal Spring	Rats (n not reported)	1.0	3.3	2.3	3.30	Stark *et al.* [67]

Several non-device based studies of mechanotransductive enterogenesis in rat models are reported in which the infusion of saline [63] and polyethylene glycol (PEG) [61] into isolated bowel segments induced longitudinal and radial loads. Puapong *et al.* [63] reported lengthening the small bowel of rats (n = 7) by a factor of 1.32, from 3.1 cm to 4.1 cm. Okawada *et al.* [61] infused PEG into isolated segments of small bowel in mice (n = 8), which created an osmotic gradient that drew fluid into the bowel, leading to increase in bowel segment length by 17.9%. Radial bowel growth due to the application of pressure (rather than pure bowel tension) induced an increase of bowel diameter by 74.3%.

1.2.1.2. Comparison of Medical Results in Rabbit and Rat Studies

Table 1.4 summarizes the statistically significant morphological differences, differences in total enzyme activity, differences in the concentration of DNA, RNA, and protein, and differences in cell proliferation, all when comparing the lengthened tissue segments to appropriate control segments.

The morphology of the rabbit and rat segments were largely preserved. However, almost all studies reported statistically significant thickened muscle layers due to cell hypertrophy (enlargement). Okawada *et al.* also reported an increase in muscle layer thickness, but it was not statistically significant. The significance of this commonality across enterogenesis studies and animal models is not known. However, the overall preservation of other morphological features is a positive indicator of true growth. Where reported, total enzyme activities were mostly increased, which also suggests the true growth of bowel tissue because of the associated increase in total absorptive capacity of the tissue. No statistically significant changes in the concentration of DNA, RNA, or protein were recorded, which suggests the preservation of tissue cellularity - meaning the density of cells was not different and therefore the tissue was not merely stretched. Lastly, the measurement of cell proliferation was reported in two studies, one of which described a large increase in the number of proliferating cells, another indication that true tissue growth occurred. Ultimately, the culminating conclusion to these studies is that the small bowel of rat and rabbit models is mechanosensitive and that the application of tension induces the true growth of healthy bowel tissue. More importantly, these results hint at the feasibility of the mechanotransduction approach for clinical application in humans. However, there is a large gap between these initial studies with small animal models and the development of a clinical treatment.

Table 1.4. Statistically Significant Medical Results of Rabbit and Rat Enterogenesis Studies. Common tissue evaluation metrics included morphological changes, enzyme activity, cell proliferation, and RNA, DNA, and protein concentrations. In all studies using a mechanical lengthening device (excludes Okawada *et al.*), an increase of muscle layer thickness due to hypertrophy was reported. Where reported, total enzyme activity increased, cell proliferation stayed the same or increased, and the concentrations of DNA and protein did not change. Although the medical significance of the increased muscle layer thickness is not known, these results support the feasibility of a mechanotransductive treatment to SBS in small animal models. (+), (-), and (NC) denote an increase, a decrease, and no significant change, respectively.

Author	**Morphological Changes**	**Total Enzyme Activity**	**DNA, RNA, and Protein Concentration**	**Cell Proliferation**
Printz *et al.*	Muscle Thickness (+) Villus Width (+)	Not Reported	DNA (NC) Protein (NC)	No Change
Park *et al.*	Muscle Thickness (+)	Lactase (NC) Alkaline Phosphatase (+)	Not Reported	Not Reported
Safford *et al.*	Muscle Thickness (+)	Lactase (NC) Sucrase (+) Maltase (+) Palatinase (+)	Not Reported	Not Reported
Shekherdimian *et al.*	Muscle Thickness (+) Villus Height (-)	Not Reported	Not Reported	Not Reported
Stark *et al.*	Muscle Thickness (+) Crypt Depth (+)	Not Reported	Not Reported	Not Reported
Stark *et al.*	Muscle Thickness (+) Crypt Depth (+)	Not Reported	Not Reported	Not Reported
Puapong *et al.*	Muscle Thickness (+)	Lactase (+) Alkaline Phosphatase (+)	Protein (NC)	Not Reported
Okawada *et al.*	Crypt Depth (+)	Not Reported	Not Reported	Increase

1.2.2. Potential Advantages of the Mechanotransductive Approach

The mechanotransductive approach to small bowel lengthening, if proven feasible for treating SBS in clinical trials, has important advantages compared to surgically lengthening procedures and transplants. Both the Bianchi Procedure and STEP require dilated segments of small bowel to be present in the patient. Although dilated bowel segments are common with SBS patients, the extent of dilation and length of the dilated portion limit the net increase in length resulting from the reconstruction. The net increase in length induced by tensile loading will be limited only by the extension capability of the bowel extender or possibly by physiological limitations, if they

exist. Thus, greater bowel lengthening may be possible with the mechanotransductive approach. Both the Bianchi Procedure and STEP are invasive and require lengthy sutures lines, from which enteral contents may leak, causing a cascade of complications. These complications are not fundamentally associated with the mechanotransduction approach, because given the right technology, a bowel extending device may be implanted through the upper GI tract and not require piercing the bowel to apply tension. Compared to transplants, the main advantage of the mechanotransduction approach is that the increased length of small bowel is the patient's own tissue, so there is no risk of tissue rejection and no need for long-term immunosuppressive medication.

1.3. Research Issues

Despite encouraging experimental results with small animal models, there remains a long path to clinical trials of the mechanotransductive approach from both a technological and a medical standpoint. The prior results suggest that the large growth increases were not the result of stretching/yielding small bowel tissue, but rather that actual tissue growth was induced. Furthermore, the health and functionality of the tensioned tissue segments remained consistent or increased compared to appropriate controls. However, these studies were completed with small animal models. Thus, the applicability of their results to humans is limited. Several key medical studies are necessary to begin considering clinical trials based on the mechanotransductive approach.

The selection of an appropriate animal model with relevant physiological and anatomical similarities to humans must be made to conduct studies bearing greater clinical relevance. Anatomically, the GI tract components of large animals such as pigs, goats, sheep, and cows are closer in size to humans than rats and rabbits. However, goats, sheep, and cows are ruminants - animals with considerably different digestive components within their stomach that enable them to process plant-based food. Unlike ruminants, the digestive physiology of pigs is very similar to that of humans [69]. The gut microbiome of pigs also shows great similarity to that of humans, making pigs and humans susceptible to many of the same enteric pathogens [70]. Most importantly, in the context of this dissertation, preterm pigs are an important clinical model for studying the natural growth of the GI tract in preterm infants [71]. Even with these advantages, studies of mechanotransductive enterogenesis have not be reported with porcine animal models.

The gap between prior research studies of enterogenesis with small animal models and clinical trials spans five key areas of research requiring the use of clinically relevant porcine animal models: one, establishing the clinical feasibility and potential of the treatment approach; two, developing the treatment approach; three, designing and creating enterogenesis devices for studying mechanotransductive enterogenesis; four, investigating safe and reliable small bowel tissue attachment approaches; and five, developing a clinically relevant device technology and tissue expansion approach.

1.3.1. Treatment Feasibility and Potential

The mechanotransductive response of small bowel tissue in clinically relevant animal models, such as pigs, must be demonstrated by inducing healthy bowel growth via the application of tensile force. The clinical potential for the treatment will depend on the ability to lengthen tissue by large expansion factors of growth, because many patients with SBS have very little remnant bowel. Furthermore, as the bowel lengthens by large expansion factors, the mesentery must increase its vascularity to support the growing tissue with blood. Angiogenesis, or blood vessel growth, within the mesentery of the tensioned segments has not been reported in prior studies, but it is certainly important for the health of the small bowel because if the blood supply becomes insufficient as the bowel lengthens, ischemia[29] and necrosis[30] may develop. Thus, the demonstration of large expansion factor growth and mesenteric adaptation with porcine models is a key step to the development of mechanotransduction-based treatment approaches.

1.3.2. Treatment Development

To develop the treatment, it is important to understand how much load can safely be applied to the tissue, how quickly the tissue can grow, and the effect of different tissue expansion strategies on the growth rate and health of porcine small bowel tissue. Prior research studies have not explored these important aspects of small bowel growth in small animals or more clinically relevant animal models. However, exploring these issues is key to uncovering effective methods of exploiting mechanotransduction safely and providing guidelines for how to quickly induce the

29 Ischemia: Reduction of blood flow to tissue
30 Necrosis: Tissue death

growth of healthy bowel, leading to shortened implantation periods, lower risks of complication, lower costs, and better outcomes.

Examples of tissue expansion profiles include constant displacement rate, constant load, and ramping displacement rate, to name a few. In the rabbit study with the Internal Screw Device and the rat studies with the External Screw Device, the tissue expansion profile used was a constant impulsive daily displacement rate profile, where the net expansion of the tissue was increased by the same amount each day. Although simple to execute, this expansion profile may not be well-suited for efficiently inducing small bowel growth because the displacement rate must be set conservatively to prevent the application of injurious loads on the bowel. In the rat studies with the Intraluminal Spring, the tissue expansion profile was based on the application of a linearly decreasing tensile load generated by a NiTi spring. However, other displacement profiles may be more effective, such as a ramping profile, where the tissue is expanded by greater daily displacements as the implantation progresses, or a constant profile, where small expansions are spaced evenly during the distraction period. Furthermore, constant, ramping, and impulsive load profiles may be applied to achieve healthy and functional porcine small bowel growth rapidly.

1.3.3. Device Technologies for Studying Mechanotransductive Enterogenesis

To conduct experiments establishing the feasibility of the mechanotransductive approach and further developing the treatment in porcine animal models, the current state of the art in enterogenesis devices is not sufficient. The advantages and disadvantages of the Internal Screw Device, External Screw Device, and Intraluminal Spring are shown in Table 1.5. The reason these devices cannot be used to conduct feasibility studies in porcine animal models is that they cannot be simply scaled up for porcine models due to safety concerns. To develop treatment approach guidelines and explore methods of efficiently exploiting mechanotransductive growth, a more sophisticated enterogenesis device is needed with displacement control, displacement measurement, and bowel tension measurement.

Table 1.5. Advantages and Disadvantages of Prior Enterogenesis Devices.
The prior enterogenesis devices, designed for rabbits and rats, have several important features in common. Although they all promote high expansion factor growth, they cannot be scaled up for large animal studies, do not measure the applied tensile load, and do have load control (although the loads applied by the Intraluminal Spring can be limited by the spring design). For these reasons, new enterogenesis devices were developed to enable studies with porcine animal models, which are clinically relevant.

Feature	**Internal Screw Device**	**External Screw Device**	**Intraluminal Spring**
Animal model designed for	Rabbits	Rats	Rats
Can be scaled up for large animal studies	No	No	No
Displacement measurement (without imaging technology)	Yes	Yes	No
Displacement control	Yes	Yes	No
Load measurement	No	No	No
Load control	No	No	Somewhat Yes
Fully implantable	No	No	Yes
Implantable in continuous bowel	No	No	No
High Expansion Factor	Yes	Yes	Yes

1.3.3.1. Scalability for Enabling Feasibility Studies with Porcine Animals Models

The Internal Screw Device, External Screw Device, and Intraluminal Spring designs were considered for demonstrating the feasibility and potential of the mechanotransductive treatment approach in porcine models, but safety concerns for the health of the animal model have arisen due to the strength and activity level of porcine models. The Internal Screw cannot simply be scaled up for feasibility studies with porcine models because the screws are required to protrude through the abdomen. The risk of the animal model injuring itself with rigid structures extending

from the body is high because the animal likely to catch the structure on a feature of the pen, thrust its body against a wall of the pen in an attempt to scratch, or kick the structure with its hind legs. These actions would not only potentially harm the animal, but also lead to poor experimental outcomes because the bowel tissue may tear as a result of the impulsive external loading. To overcome this challenge, the porcine animal models cannot be immobilized because it is impractical and against regulations set by the University Committee on the Use and Care of Animals to stantion pigs. Like the Internal Screw Device, the External Screw Device cannot be safely scaled up for feasibility studies with porcine models because the device fundamentally has rigid external features that pose health risks and would not be tolerated by porcine animal models. Although the intraluminal spring has no extracorporeal structures, there are concerns with scaling it up for large animals. The initial studies reported that the springs could sometimes buckle, which later studies fixed by placing a concentric guide wire down the center of the spring. The guide wire must be stiff enough to prevent spring buckling and long enough to support the fully extended spring. Thus, the guide wire poses unacceptable health risks, such as bowel perforation, for strong, large, and physically active porcine animal models. Also, the uncontrolled nature in which the spring expands is a cause for concern, because it could potentially damage the tissue. Additionally, the intraluminal spring would be implanted in an isolated segment of small bowel with both ends surgically closed, requiring the implantation of mucous drainage catheters that can lead to surgical complications. As a result, none of the current enterogenesis device designs are suitable for studying feasibility in large animal models.

1.3.3.2. Suitability for Enabling Studies to Develop Treatment Approach Guidelines

The prior enterogenesis devices have both significant advantages and disadvantages in the context of further developing the mechanotransductive based treatment approach in clinically relevant porcine models. To understand how much load can safely be applied to the tissue, how quickly the can tissue grow, and what is the effect of different tissue expansion strategies on the health and growth rate of the tissue, an enterogenesis device for porcine models with displacement control, displacement measurement, load control, load measurement and full implantability is required. None of the current enterogenesis devices have these capabilities and cannot be scaled up for porcine models. Therefore, new enterogenesis device technologies designed to explore these issues is required.

1.3.3.2.1. Displacement Measurement and Control

The measurement and control of displacement is an important capability for enterogenesis devices from a safety standpoint (to prevent injurious increases of tissue expansion), but also for enabling experiments where differing displacement rates and profiles are investigated. The Internal Screw Device and External Screw Device allow for simple displacement measurement and control by recording the numbers of screw turns made by medical personnel. Displacement measurement with the Intraluminal Spring is not possible without the use of radiographs, which can be difficult to interpret because of device orientation and the lack of a scale, and there is no control of displacement. This lack of displacement control limits the scope of research studies that can be undertaken with the Intraluminal Spring, because the effect of varying displacement rates and profiles cannot be rigorously explored.

1.3.3.2.2. Tensile Load Measurement and Control

The measurement and control of bowel tension is another important enterogenesis device capability for further developing the treatment approach. However, none of the devices are instrumented to enable load measurement, which is important for avoiding the application of injurious loads and for enabling experiments that explore the effect of the load profile on the rate and health of tissue growth. The Internal Screw Device and External Screw Device could both instrumented to monitor force, but this approach was not considered because they cannot be safely scaled up for porcine studies. The Intraluminal Spring can be designed to produce a nearly constant load as a result of the super-elasticity property of NiTi. Thus, there is the potential to apply different constant tensile loads to small bowel by carefully designing the spring. However, this is not true load control, because the application of different load profiles is not possible.

1.3.3.3. Summary Evaluation of Research Enterogenesis Devices

Although important for studying the mechanotransductive enterogenesis of small bowel in small animal models, prior enterogenesis devices do not enable studies critical for supporting the clinical application of mechanotransductive enterogenesis in large animal models. As shown by Table 1.5, none of the prior art are scalable for studies with porcine animal models to address clinical feasibility. Furthermore, although the internal and external screw device have displacement control and measurability, none of the devices are able to record the applied bowel tension in real-time. Load measurement, displacement measurement, and displacement control are

necessary features for enterogenesis devices that enable studies to development treatment approach guidelines. As a result, new enterogenesis devices designed for porcine animal models are required to conduct studies of small bowel growth bearing clinical relevance.

1.3.4. Attachment Methods

The safe transfer of load from the extending mechanism to the bowel lumen remains a challenge. In prior research studies on mechanotransductive enterogenesis, two primary tissue attachment approaches have been used: end abutting attachments, and attaching through the lumen with sutures. Although these attachment methods were suitable for research, there are significant disadvantages that limit their extension to clinical applications. Thus, new approaches for attaching to small bowel are needed for clinical applications.

To induce longitudinal small bowel growth, an expansion mechanism must be coupled with attachments that can safely and reliably transfer load from the device to the tissue. Prior research with the External Screw and Intraluminal Spring relied on attachment by end-abutment, an approach where the ends of the device push on one or two blinded ends of an isolated small bowel segment. Although shown to be reliable, this approach is not clinically acceptable because it requires the removal and reinstatement of the grown bowel segment into GI tract – operations that require significant portions of bowel to be discarded to create and take down the surgical connections of the bowel. Additionally, attachment by end-abutment precludes the ability to implant and remove enterogenesis devices by non-invasive surgical procedures.

Sutures were used to transfer load from the Internal Screw Device to rabbit small bowel in the first studies of mechanotransductive enterogenesis with small animal models. The authors reported that the sutures cut through the bowel wall without causing perforation, disconnecting the Internal Screw Device from the rabbit small bowel. Similarly, traction sutures are placed in the proximal and distal esophageal pouches and pulled on to create tension in the tissue and induce growth for the treatment of long-gap esophageal atresia. The difficulty of this technique, known as the Foker Method, is that the traction sutures cut through the esophageal wall, causing esophageal leakage and requiring an additionally thoracotomy to replace the sutures [72]. As a result, the reliability and safety of the suture-based attachments for tensioning soft tissue has been demonstrably poor.

Thus, a better attachment approach is required for the clinical application of mechanotransductive enterogenesis. However, there are significant challenges that make the development of safe and reliable intraluminal attachments non-trivial:

1. the bowel lumen is very slippery and lined with cells that continuously slough off,
2. the attachments must be easily maneuvered through the bowel for implantability, but simultaneously be able to grip the bowel lumen,
3. bowel obstruction must be avoided,
4. the attachments should be robust to peristalsis and radial bowel adaptation, and
5. safe attachment to the bowel lumen is difficult due to the delicate nature of the tissue and the risks of tissue ischemia and perforation.

Because of the compliance of small bowel tissue, attachment by the application of pressure to an area of the bowel lumen can potentially stop blood from perfusing that area, leading to ischemia and subsequent necrosis and/or perforation. Thus, attachments have a tradeoff between their ability to transfer load and the health risks their use poses. However, this tradeoff must be overcome to realize clinically applicable attachments, because both tissue health and attachment performance are critical. In addition to the need of the attachments to reliably and safety grip bowel tissue, they must also be able switch between attached and detached states to facilitate their implantation, removal, and purposeful repositioning.

1.3.5. Clinical Device Development

Lastly, current enterogenesis devices were designed for researching mechanotransductive growth in small animal models and they cannot be safely scaled up for research with large animals or for clinical trials. With respect to clinically applicable enterogenesis devices, there is no prior art. Thus, technologies for correcting short bowel syndrome designed for clinical applicability are needed.

For a clinically applicable device, greater designs constraints are present compared to research-orientated devices. The most important differences are the need to be able to implant the device in a continuous portion of the small bowel (by non-invasive surgical techniques) rather than within an isolated segment, the greater constraints on the form of the device, greater lengthening capabilities to enable the treatment of severe cases of SBS, and the enhanced emphasis on device

safety features including applied tensile load measurement, displacement control, and displacement measurement.

None of the current enterogenesis device technologies can be implanted in a continuous segment of small bowel by non-invasive surgical techniques. The External Screw Device and the Intraluminal Spring cannot be implanted in continuous bowel because they attach to the small bowel by end-abutment, an approach that requires the isolation of the distracted tissue segment. The Internal Screw Device was designed to apply tension to a segment of continuous small bowel, but the device cannot be implanted with non-invasive surgical techniques because its implantation requires a laparotomy. Constraints and guidelines concerning clinical enterogenesis device form have not been explored in prior studies. Device form encompasses coupled parameters including device length, rigidity and curvature; device diameter; the proximal and distal device/tissue interface; and the local feature contours of the device. Prior studies have also not described required tissue lengthening capabilities to treat severe cases of short bowel syndrome. However, this is likely because every patient with SBS is different and will thus respond to small bowel tissue lengthening to a different extent. Lastly, because prior enterogenesis device were designed primarily for research purposes, they to do reflect an emphasis on device safety features such as the capability to monitor the applied small bowel tension.

1.4. Research Goals and Objectives

The goal of this research is to explore technological approaches for a promising and novel treatment method of short bowel syndrome based on mechanotransduction. Four key research objectives have been identified toward to the achievement of this goal:

1. **Treatment Approach Feasibility and Potential.** Investigate the potential for inducing large net growth, large expansion factor growth, and inspect the mesentery for an increase in the vascularity to evaluate the feasibility of mechanotransduction for correcting short bowel syndrome and to support further research into the technologies for and the development of mechanotransduction-based treatment approaches.
2. **Treatment Development.** Create technologies and perform studies to determine the upper bound of safely applied bowel tension, compare the effect of applying different tissue expansion profiles on tissue growth and explore the limits of the maximum small bowel expansion rate to

develop the best practices and methods for safely and effectively exploiting mechanotransduction.

3. **Tissue Attachment.** Develop clinically relevant tissue attachments for the safe attachment and detachment of an expansion mechanism to the small bowel. Identify the risk of surgical complications associated with a range of attachment approaches, including perforation and ischemia, and measure their attachment and detachment performance.
4. **Clinically Relevant Device.** Develop and demonstrate a clinically relevant enterogenesis device and treatment method for pediatric and adult SBS by demonstrating very high net bowel growth. The *in vivo* validation of the device with porcine models must produce medical results for promoting clinical trials by achieving high expansion factor growth backed by analysis of the tissue to demonstrate its health and functionality.

1.5. Summary of Research Approach

To meet the goal of this dissertation, a similar research approach was taken for objectives one, two, and four. The approach taken was as follows: based on the objective, design an enterogenesis devices with pertinent functionality, fabricate the device, validate and/or characterize the device performance on the benchtop, and conduct *in vivo* medical studies to further validate the performance of the device and answer objective-specific questions about mechanotransductive small bowel growth. To meet the third objective on tissue attachment approaches, a large set of attachment approaches were downselected through a series of *in vivo* studies that evaluated their attachment performance, detachment performance (where applicable), and the health risk they impose with respect to bowel ischemia and perforation.

1.5.1. Objective One: Treatment Approach Feasibility and Potential

To establish the feasibility of the mechanotransductive approach and demonstrate its potential for correcting short bowel syndrome, the tasks of this objective were to explore the potential for high net growth, large expansion factor growth, and to observe the adaptation of vasculature in the mesentery. To achieve this, a three-stage telescoping curvilinear hydraulic device was developed and used to induce bowel growth in a series of *in vivo* studies. The housing and three telescoping stages of the Curved Hydraulic Device were curved to reduce stress on the mesentery, which is a thin membrane supplying the support structure for the vasculature feeding the bowel. Additionally,

the curved design also reduced the end-to-end length of the device, allowing it to fit more readily in the limited peritoneal cavity. Small bowel naturally loops as a result of radial mesenteric forces. Thus, a linear enterogenesis device causes more stress on the mesentery than a curved device. Because the Curved Hydraulic Device has greater extension capabilities compared to other enterogenesis devices, its curvilinearity was especially important to reduce stress on the mesentery. The goal, however, was not to completely eliminate stress on the mesentery, as it must adapt and grow along with the small bowel tissue it supports.

During experimental studies, the Curved Hydraulic Device was implanted in an isolated (from the continuous GI tract) segment of small bowel known as a Roux limb. Therefore, the device posed no risk of bowel obstruction because enteral contents do not pass through the Roux limb. The device was actuated by the injection of water from an external syringe, via a transdermal hydraulic line passing through an ostomy formed at the proximal end of the Roux limb. Fluid was gradually forced into the Curved Hydraulic Device from the external syringe, making the stages of the device extend, which in turn applied growth inducing tension to the small bowel. At the end of the implantation period, tissue samples were taken to demonstrate the true growth of small bowel tissue by evaluating the morphology, histology, cell proliferation, and the neovascularization of the mesentery supporting the growth segment.

1.5.1.1. Design Considerations

Several considerations were important for the design of the Curved Hydraulic Device, including specifying an expansion factor target, designing the components to not yield due to external loading, and determining the dimensional constraints imposed by the size of the porcine abdominal cavity, bowel lumen diameter, and the height of the mesentery (for determining the curvature of the device).

1.5.1.2. Prototype

To prototype the Curved Hydraulic Device, three main tasks were identified: fabricate the housing and three telescoping stages, develop a sliding sealing method, and develop an attachment method for transferring load from the device to the tissue. The resulting prototype was composed of a housing and three stages that were made from 316 stainless steel and manually curved around a 9 cm radius mandrel. The housing and stages were sealed with soft butyl rubber seals from medical syringes, because curving the stages and housing caused the components to have an

elliptical cross section that could not be sealed with conventional O-rings. To transfer load to the small bowel, two circumferential rings of sutures were placed at both ends of the device during the implantation procedure. In some trials, the sutures were reinforced with denatured pig skin or denatured human skin to improve the reliability of the attachments.

1.5.1.3. Validation and Characterization

To prepare for *in vivo* studies, the performance of the Curved Hydraulic Device was characterized by experimentally finding the relationship between the input fluid volume and the resulting device displacement. The three telescoping stages of the device have decreasing cross-sectional areas. Thus, for a fixed volume of injected fluid, the stages displaced different amounts. Additionally, the order in which the stages extend was not consistent. Therefore, there was not a one-to-one relationship between amount of fluid injected and the device displacement. However, the range of possible displacements as a function of the injected fluid volume was found.

1.5.1.4. *In Vivo* Studies

A series of *in vivo* studies have been completed with the Curved Hydraulic Device that produced promising small bowel growth results that were corroborated by analyses of the tissue morphology, cell proliferation, barrier function, and evidence of increased vascularity with the mesentery. This series of studies was the first to quantitatively identify an increase in the vasculature of the mesentery resulting for bowel growth, which is an important finding because large increases of the bowel length must be supported by the vasculature of the mesentery. This, along with the healthy and functional growth of porcine small bowel, demonstrated the clinical feasibility of the mechanotransduction treatment method and its potential for inducing significant lengths of small bowel growth.

1.5.2. Objective Two: Treatment Development

To go beyond the demonstration of feasibility and begin discovering the knowledge needed to effectively design a clinical device and guide its usage, a new enterogenesis device with different functionality and capabilities than the Curved Hydraulic Device was developed. Further *in vivo* experiments were conducted that compared different tissue expansion strategies, explored how rapidly small bowel can be safely grown, and explored the maximum safe tension that can be applied to the tissue. To enable these experiments, a considerably more sophisticated enterogenesis

device with force instrumentation and displacement control was required. Although the Curved Hydraulic Device could be instrumented with a force sensor, the Instrumented SMA Driven Ratchet was developed because the accurate control of displacement could not be achieved with the hydraulic device due to stiction, the compliance of the hydraulic lines, and the unpredictable order in which the stages extended. In contrast, the expansion of the Instrumented SMA Driven Ratchet was gradual (each actuation extended the device by 1.2 mm), repeatable, and controlled.

Like the Curved Hydraulic Device, similar post experiment tissue analyses were performed, and the Instrumented SMA Driven Ratchet was implanted in a Roux limb during *in vivo* experiments to eliminate the risk of device-related bowel obstruction. During experiments, a wireless communication link between the Instrumented SMA Driven Ratchet and the operator enabled concurrent control of the device expansion and gave immediate feedback on the applied bowel tension and tissue displacement. When commanded from a PC running the user interface, the device completes one operation cycle of its ratcheting mechanism, applying tension to the small bowel segment and inducing growth. The measurement of the applied bowel tension was used to avoid the application of injurious loads as well as to enable experiments where the expansion of the device was guided by displacement rate and/or applied bowel tension based strategies.

1.5.2.1. Design

The Instrumented SMA Driven Ratchet is composed of two main subsystems: the ratcheting mechanism, and the data acquisition and control system. To design the SMA driven ratcheting mechanism, design guidelines for defining the ratchet pawl and rack geometries were developed to take packaging constraints, load bearing capacity, self-locking behavior, and the pawl reengagement kinematics into account. Additionally, a novel adaptation of the traditional graphical design method for SMA actuated devices called the Reset View Design Methodology was developed. In short, the design methodology visually enables the designer to understand and specify the reset, or bias, spring common to SMA actuated devices. To use the Reset View Design Methodology, the system loads on the SMA actuator needed to be predicated or experimentally determined. To achieve this, an analytical model of the force required to drive the ratcheting mechanism was developed, the safe range of applied load on the bowel was experimental characterized, and external forces due to friction were conservatively estimated.

To design the data acquisition and control system, the desired subsystem functionality was specified and the physical embodiment of the subsystem was separated into three separated components: the Bowel Extender Circuit, the Pack Circuit, and the Base Station Circuit. The Bowel Extender Circuit, which mounted directly on the device, drove the SMA wire, digitized the outputs of the force and displacement sensors, and relayed data/commands through a wired serial communication link with the Pack Circuit. The Pack Circuit, which was mounted subcutaneously or on the animal model's back, acted as the main control unit of the subsystem and communicated wirelessly with Base Station circuit, which acted as a relay between the medical operator and the Pack Circuit.

1.5.2.2. Prototype

Utilizing the Reset View Design Methodology and the design guidelines for the ratchet pawl and rack geometries, the ratcheting mechanism was designed and then fabricated mostly from rapid prototyped (SLA) components. To seal the body of the device, it was encapsulated in RTV silicone adhesive, and the rack/body interface was sealed with a Viton gasket. The components of the Bowel Extender Circuit were selected to minimize the footprint and power consumption, and the operating frequency of the wireless communication link was chosen as 433 MHz because experimental studies showed that the 433 MHz frequency had reduced signal attenuation through the tissue compared to 2.4 GHz.

1.5.2.3. Characterization and Validation

The analytical ratcheting force model, the performance of the ratcheting mechanism, and the performance of the data acquisition and control system were validated successfully on the benchtop. To verify the analytical ratcheting force model, a custom load and displacement measuring system was created that allowed for the direct measurement of force applied by the actuator as a function of stroke. The magnitude and form of the experimental data matched well (within measurement noise) with predicted values, thus validating the model. The performance of the ratcheting mechanism was validated by ratcheting against increasing static loads until the ratcheting operation cycle could not complete. The results of this experiment demonstrated the mechanism's ability to operate against up to 850 gf, well above the required specification. The data acquisition and control system was characterized and validated by calibrating the load and displacement sensors, determining the range of the wireless link, demonstrating the sufficient

capacity of the onboard battery, and by testing the stability and functionality of the subsystem in a two-week benchtop experiment where the Instrumented SMA Driven Ratchet was submerged in a saline bath held at the average internal temperature of a pig.

1.5.2.4. *In Vivo* Studies

The Instrumented SMA Driven Ratchet has been used in a series of *in vivo* studies to evaluate the performance of the device and to examine the force and growth response of the bowel to different tissue expansion strategies based on the tissue displacement rate and/or the applied tensile load. In total, three tissue expansion strategies were performed in separate experiments: Constant Rate Impulsive Displacement Control (wherein the tissue expansion was 8.4 to 9.6 mm per day and not based on the applied tension), Displacement Rate Limited Load Control (wherein the device automatically expanded every time the measured load was below 60 gf, but no faster than 1.2 mm, one actuation, per hour), and Constant Load Control (wherein the device automatically expanded every time the measured load was below 45 gf without a displacement rate limitation). In this series of studies, the rate of small bowel expansion increased significantly as the determination of when to expand the tissue was based on the applied bowel tension.

Across studies, analyses of tissue samples taken from the distracted segments indicted little evidence of serosal or muscle layer tearing, the gross preservation of morphology, maintenance of the barrier function, and similar percentages of proliferating cells (compared to relevant controls). These promising medical results indicated that the small bowel tissue underwent true growth rather than experiencing permanent yielding, and that basing the expansion of the tissue on the measured tensile load is a safe approach to rapidly growing small bowel tissue.

1.5.3. Objective Three: Tissue Attachment

Current attachment approaches for transferring load to the small bowel in research studies include end-abutment and sutures, both of which are not extendable to the clinical application of the mechanotransduction approach to correcting SBS. To safely and effectively couple the expansion mechanism to the bowel lumen in a clinical context, it is important to have attachments that are implantable in continuous bowel without causing bowel obstruction, the attachments should grip the bowel lumen during the distraction period, operate in a detached state to facilitate device implantation, removal, and purposeful repositioning, and the attachments should be designed such that they do not cause bowel perforation or ischemia. The approach to developing

a reliable and safe tissue attachment was to conceptualize a broad range of approaches, fabricate them, and evaluate their performance in a series of *in vivo* experiments.

1.5.3.1. Conceptualization and Initial Downselection

The design process was to develop and categorize a wide range of conceptual attachment approaches including End Abutment, Dilation, Impingement, Binding/Kinking, Adhesion, Clamping, and Tissue Piercing. For each approach, concepts were generated and a qualitative assessment of safety and feasible was made to reduce the number of conceptual embodiments to be designed, prototyped and experimentally evaluated. The initial downselection of the concepts was based on an assessment of manufacturability, feasibility, safety, availability, and cost, while further downselection was based on experiment studies.

1.5.3.2. Experimental Studies

The goal of the *ex vivo*[31], acute *in vivo*, and one-to-two week *in vivo* studies was to evaluate the range of attachments approaches based on attachment performance and the risk of surgical complications associated with their use. The attachment performance metrics included their ability to transfer high loads (greater than 200 gf) without slipping, their attachment reliability *in vivo* in experiments up to and exceeding one week, and their ability to facilitate surgical implantation and removal by sliding easily though the tissue lumen it their detached state. The metrics related to preventing surgical complications included the risk of bowel obstruction by enteral content blockage, the risk of tissue ischemia, and the mechanical risks of tissue perforation and tearing.

Acute *in vivo* experiments were conducted on a range of the attachment concepts to determine how well they attach, detach, and if they pose the risk of health complications like ischemia and bowel perforations and/or tears. Because *ex vivo* experiments cannot be used to determine the risk of ischemia, most attachments were evaluated in acute (less than 1-2 hour) *in vivo* experiments. Longer *in vivo* experiments were conducted to evaluate the attachment performance and potential surgical complications with a series of attachment approaches that demonstrated promise in the *ex vivo* and/or acute *in vivo* experiments. These approaches included the binding/kinking approach, the clamping approach, the tissue piercing approach with sutures, and the dilation approach with textured balloons. At the conclusion of these studies, the Dilating Fenestrated Mesh was the most

[31] *Ex Vivo*: Occurring outside of animal (within tissue removed from animal)

promising attachment for small bowel because of its ability to attach and detach from the bowel lumen in weeklong *in vivo* experiments without causing bowel ischemia or perforation.

1.5.4. Objective Four: Clinically Relevant Device

The first two objectives established the need for enterogenesis devices to conduct *research* on treatment feasibility and the methods by which the growth process and be safely exploited to quickly grow small bowel tissue in clinically relevant animal models. Thus, the design an enterogenesis device for *clinical* applications was a new design problem and prompted the reexamination of customer needs and design goals. Because the third objective concerned the development of clinically relevant tissue attachment approaches, the design of the clinically relevent device focused on the tissue expansion mechanism. The development of the clinically relevant device expansion mechanism followed the formal design process of understanding the goals of the device, developing metrics to compare different conceptual approaches, concept development, downselection, refinement, fabrication, and validation both on the benchtop and in a one week *in vivo* experiment.

The culminating final tasks of this dissertation were to integrate the expansion mechanism with the intraluminal attachments and demonstrate the performance of the device through *in vivo* experimental studies. The *in vivo* experiments were used to validate the performance of the device and to determine if the payout approach to growing small bowel is feasible. As with prior *in vivo* experiments, tissue analyses were performed to evaluate the health and functionality of the grown tissue segments.

1.5.4.1. Design

A conceptual approach based on "paying out" tissue was identified as the most advantageous approach based on a Pugh chart analysis. A key defining advantage of the payout approach is that the net growth of bowel is not limited by the length or the stroke of the device, unlike current enterogenesis device technologies. In the payout operation, tension is applied the small bowel tissue in a continuous or incremental fashion by attachments that rotate or translate lengthwise, respectively. In the continuous approach, rotating attachments continuously apply tension to the small bowel growth segment which pays out small bowel tissue from one or both ends of the device. In the incremental payout approach, bowel tension is supplied by an attachment that translates back and forth along the length of the device with each cycle paying out an incremental

length of small bowel from one or both ends of the device. An embodiment of the incremental payout approach was developed because of its compatibility with the downselected attachment. The refined concept was a compact single-stage reciprocating linear hydraulic device with the unique capability to extend and retract without requiring two hydraulic lines.

1.5.4.2. Prototype

To create an environmentally robust prototype, the Reciprocating Linear Hydraulic Device was fabricated by traditional machining techniques from a variety of non-corrosive biocompatible materials including 316 stainless steel, natural Delrin, and nylon. The stainless steel body of the device extends by 3.4 cm with driven by the hydraulic line with approximately 2cc of water. When the pressure on the hydraulic line is released, a compression spring within the device retracts the housing back to its original position. Because the prototype could reciprocate and the attachments could actively switch between attached and detached states, the integrated prototype enabled the experimental evaluation of the payout approach's viability.

1.5.4.3. *In Vivo* Studies

In Vivo studies were conducted to validate the performance of the device and to demonstrate the payout approach to small bowel lengthening. Both results hinged of the accurate measurement of tissue growth significantly exceeding the stroke of the device and on the medical tissue analyses. To measure the macro-scale tissue growth, evenly spaced tissue marking sutures placed during the implantation were measured at the explant and compared. However, to use tissue marking sutures, the length of the experiment had to be limited because sutures become difficult to recover in experiments exceeding one week (they slip out of the tissue). The tissue analyses included an examination of tissue histology, morphology, and epithelial cell proliferation, all of which indicated the true growth of healthy small bowel tissue exceeding the 3.4 cm stroke of the Reciprocating Linear Hydraulic Device.

1.6. Summary of Contributions

This research has made important contributions to the disciplines of medical science, surgery, and engineering. The major medical and surgical contributions include establishing the clinical feasibility of the mechanotransductive treatment approach, the determination of the maximum safe tensile small bowel tissue load, the comparison of displacement and tension-based tissue expansion

profiles, and the viability demonstration of the payout approach to growing small bowel tissue. The medical studies leading to those contributions were enabled in large part by concurrently made engineering contributions, which include the three novel enterogenesis device architectures, the Reset View Design Methodology for designing shape memory alloy driven devices, the ratchet-pawl force interaction model, the *in vivo* tissue tension measurement system, and the Dilating Fenestrated Mesh intraluminal tissue attachment. All contributions and findings have been organized into four themes: medical treatment, device innovation, experimental methodologies, and mechanical device/tissue interaction.

1.6.1. Medical Treatment

This dissertation makes critical contributions toward the development of the mechanotransduction-based treatment for correcting short bowel syndrome. Most importantly, this dissertation establishes the feasibility of the treatment approach in clinically relevant porcine animal models. Additionally, experimental studies comparing tissue expansion strategies based on tissue displacement rates or/and applied tensile load were conducted with the Instrumented SMA Driven Ratchet. These studies showed that basing the expansion of bowel tissue on the applied tensile load results in much higher rates of expansion, which can clinically lead to a shorter duration of treatment, reduced complication risks, lower costs, and an overall better quality of patient care. Lastly, the medical viability of tensioning and relaxing the same segment of bowel tissue multiple times to induce high fold growth is demonstrated, supporting the design of ultra-compact enterogenesis devices that can enable non-invasive surgical techniques.

1.6.2. Device Innovation

Three actuation architectures with unique features and functionality have been developed to enable studies of mechanotransductive growth with porcine animal models, the Curved Hydraulic Device, the Instrumented SMA Driven Ratchet, and the Reciprocating Linear Hydraulic Device. Although these enterogenesis were designed to be compact and apply loads suitable for inducing bowel growth, their designs can be scaled to develop actuators for applications requiring higher force and stroke capabilities.

To design the Instrumented SMA Driven Ratchet, the Reset View Design Methodology and an analytical model of the ratchet rack and pawl force interaction were developed. Although created for the design of a compact SMA driven ratcheting mechanism, the Reset View Design

Methodology is a general graphical approach for designing SMA actuators biased by a reset element that greatly facilitates the selection of the reset element. Similarly, the ratchet rack and pawl force interaction model is scalable, making the model useful for designing a large range of actuated linear ratcheting mechanisms.

1.6.3. Experimental Methodologies

This dissertation makes contributions and findings that improve experimental methodologies for studying mechanotransductive enterogenesis. Contributions include the development of techniques for measuring net small bowel growth with marking sutures and quantifying mesenteric neovascularization using 3D reconstructions of the tissue, both important metrics for establishing the feasibility of mechanotransductive bowel lengthening approaches.

1.6.4. Mechanical Device / Tissue Interaction

This dissertation makes important contributions and findings regarding the mechanical device/tissue interaction, including the determination of the maximum safely applied bowel tension, methods for attaching to bowel tissue, and important considerations for designing the form of enterogenesis devices. The determination of the maximum safely applied bowel tension was critical for safely conducting experiments exploring high rates of healthy bowel growth. Furthermore, the methods used to determinate the upper limit can be repeated for clinical applications and used to prevent over tensioning the remnant bowel of SBS patients. A novel attachment approach for transferring load to small bowel for the correction of SBS is a significant contribution because its use can be extended to a number other medical applications such as improving endoscopic maneuverability, anchoring an instrument within large blood vessels to accurately place stents or perform endovascular coiling, and applying tensile load to the esophagus for the treatment of long-gap esophageal atresia. Many of the findings of this dissertation relate to the importance of the device form. The considerations for and relationships between length, rigidity, curvature, diameter, tissue interfaces, the local feature contours are important to understand in order to design safe enterogenesis devices. The findings here were developed over the course of this dissertation through many experiences in the operating room with porcine animal models.

1.6.5. Impact

In sum, the contributions of this dissertation lay the complete engineering and medical foundation for the design and usage of technologies for correcting short bowel syndrome by mechanotransductive enterogenesis. The mechanotransductive approach to lengthening remnant small bowel has significant advantages compared to surgical restructuring approaches and transplants. Thus, realizing the clinical potential for this novel and promising treatment approach promises to improve the quality of care for SBS patients and ultimately save lives.

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CHAPTER TWO. TREATMENT FEASIBILITY STUDIES WITH A CURVED HYDRAULIC DEVICE

Unfortunately, the current management and treatment methods for short bowel syndrome are associated with high rates of complication, morbidity, and mortality. A potential new treatment approach based on mechanotransductive small bowel growth is a promising alternative to surgical bowel lengthening and bowel transplant, but its clinical feasibility is yet undemonstrated in clinically relevant animal models. To establish the feasibility of the treatment approach, it is important to complete studies with clinically relevant animal models where large amounts of functional and healthy small bowel tissue are grown. Large net growth and large expansion factors of growth are important to demonstrate with clinically relevant animal models, such as pigs, because SBS patients may have very little remnant bowel following major small bowel resection. In addition, observing adaptation of the mesenteric vasculature is important because it is needed support the greater lengths of small bowel tissue.

Research-oriented devices for studying tension induced small bowel growth in rabbits and rats have been successful, but the devices were designed for small animal models and could not be scaled up for studies with larger and more clinically relevant animal models such as pigs. The external [3–5] and internal [6] screw devices are not fully implantable and have rigid extracorporeal features that pose health risks for stronger, more active, and larger animal models. While the intraluminal spring [7–9] is fully implantable, its use in porcine models poses risks as well due to the requirement of draining the isolated bowel growth segment of mucous, and the uncontrolled nature of the spring's expansion.

Recently at the University of Michigan, an initial study [2] was conducted on the clinical feasibility of mechanotransductive enterogenesis with porcine models that used a simple linear two stage hydraulic device (Figure 2.1). The device is composed of a housing and two telescoping stages that extend as working fluid is injected via a transdermal hydraulic line with a syringe. As the linear hydraulic device extends, its ends abut the suture lines of the isolated bowel segment within which it is placed, applying tension to the tissue and inducing growth. As with the rabbits and rats, the porcine small bowel was proven mechanotransductive, achieving an extension ratio of 1.45 with only eight days of applied distractive forces in an initial study [2], as well as demonstrating the maintenance of bowel length and function upon restoring distracted segments back into the continuity of the GI tract in a subsequent study where the expansion factor was 2.03 [1]. These studies investigated a variety of functionality and health metrics of the distracted tissue segments including the tissue morphology, enzyme activity, barrier and transport function, the percentage of proliferating cells, and bowel motility. The results of these evaluations suggested that the distracted segments preserved tissue function and health, as well as increased the percentage of proliferating cells. Thus, the initial studies with clinically relevant models were very promising because true growth of small bowel was achieved without a loss of function.

Although these studies are very encouraging, an even greater lengthening of the small bowel is needed to demonstrate the potential efficacy of this treatment approach for treating extreme cases of SBS. Furthermore, small bowel growth experiments to demonstrate high expansion ratio growth and mesenteric adaptation are important for the clinical application of the mechanotransduction based approach. Prior bowel growth studies have not reported any observations of mesenteric growth and adaptation, but the growth and remodeling of blood vessels

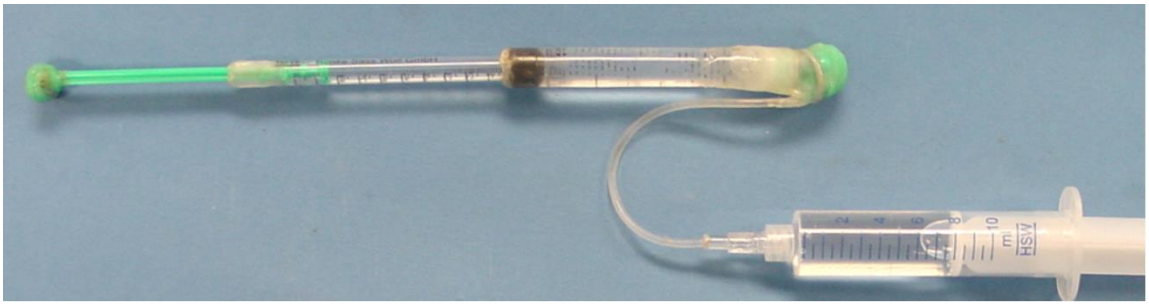

Figure 2.1. Linear Hydraulic Device (shown extended).
Used in early studies [1,2] of mechanotransduction at the University of Michigan, a two-stage linear hydraulic device made of medical syringes is shown.

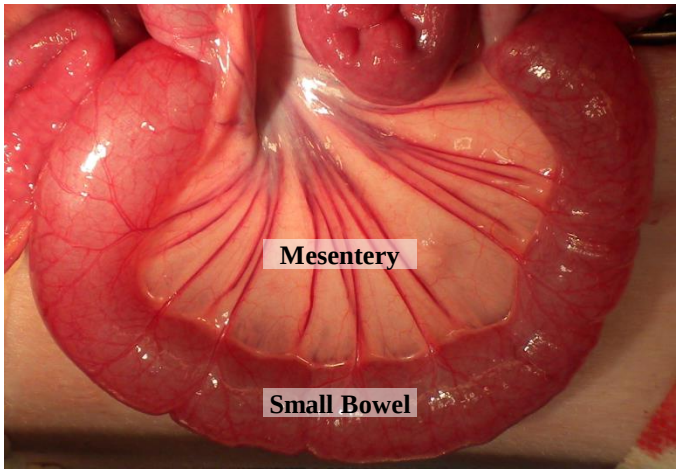

Figure 2.2. Porcine Small Bowel Loop with Mesentery.
The influence of the mesenteric load on the small bowel causes it to bend naturally.

within the mesentery is critical for supporting the increased length of bowel tissue, particularly as greater expansion factors are sought to demonstrate the potential of the treatment approach. To increase the lengthening capability of the previously used Linear Hydraulic Device, perform experiments with high growth ratios, and observe how the mesentery adapts when high growth ratios are achieved, the Curved Hydraulic Device has been developed. Two important reasons allow for greater lengthening of the Curved Hydraulic Device as compared with the linear hydraulic device. First, the space of the abdominal cavity is limited. Thus, extending along curved path increases the potential net growth of small bowel. Second, a curved device reduces mesenteric stress, allowing for greater displacement due to the decreased chance of complications such as mesenteric tears and/or ischemia. As shown in Figure 2.2, the mesenteric forces on the bowel are radially inward, causing the tissue to curve. By developing a curved hydraulic device, extraneous forces on the mesentery can be minimized during the implantation and expansion of the device.

The objectives of this chapter are to evaluate if large net bowel growth is possible without loss of bowel health and function, if unprecedented high expansion factors of growth are possible, and if the mesentery adapts to meet increasing demands for blood flow by the growth and remodeling of blood vessels that support the increasing length of the small bowel. To enable experiments exploring these objectives, a new Curved Hydraulic Device was developed to better fit within the porcine abdominal cavity, reduce extraneous mesenteric stress, and provide greater expansion performance compared to the Linear Hydraulic Device. This chapter describes the architecture and

operation of the Curved Hydraulic Device, the design and fabrication of the prototype, its benchtop performance validation, and its *in vivo* use for experimental bowel growth studies in porcine models. The Curved Hydraulic Device has been used in a series of *in vivo* experiments to determine the feasibility of mechanotransductive growth in clinically relevant animal models, where the tissue of the distracted segments was evaluated for indications of true growth rather than stretching. To guide these studies, experimental plans were developed for surgically implanting, expanding, and surgically removing the Curved Hydraulic Device after one to three weeks of tissue distraction. In the series of experiments, the expansion rate was set to impose an impulsive displacement prolife, expanding the device twice a day. The medical evaluations included examining the tissue morphology, percentage of proliferating cells, barrier function, and observing the mesentery for increased vascularization. Despite challenges related to securely attaching the device to the bowel wall, strong growth results and the observation of mesenteric adaptation have suggested the feasibility and potential of the mechanotransductive treatment approach for correcting SBS.

In addition to demonstrating the feasibility of the mechanotransduction-based treatment approach and laying the foundation for further research, these studies have also made more general engineering, medical analysis, and surgical contributions. The multistage, telescoping, curved hydraulic device architecture is a unique and novel actuator with potentially wide ranging applications. To record the adaptation of mesenteric vasculature, a new method of visualizing the vasculature and quantifying the volume of blood vessels within the tissue was utilized for the first time with porcine mesentery. And furthermore, insights have been made toward solving the general surgical challenge of reliably securing sutures under tension to soft tubular tissues like the esophagus and small intestine.

2.1. Curved Hydraulic Device Design

To investigate the potential for inducing large net growth and large extension ratio growth, the Curved Hydraulic Device concept was designed and developed for *in vivo* studies with porcine animal models. The choice of animal model greatly affects the design of the Curved Hydraulic Device and the clinical applicability of experimental results. While no animal model will completely mimic a human, porcine models have been chosen for studying mechanotransductive small bowel growth because the internal anatomy of a pig is very similar to that of a human, they

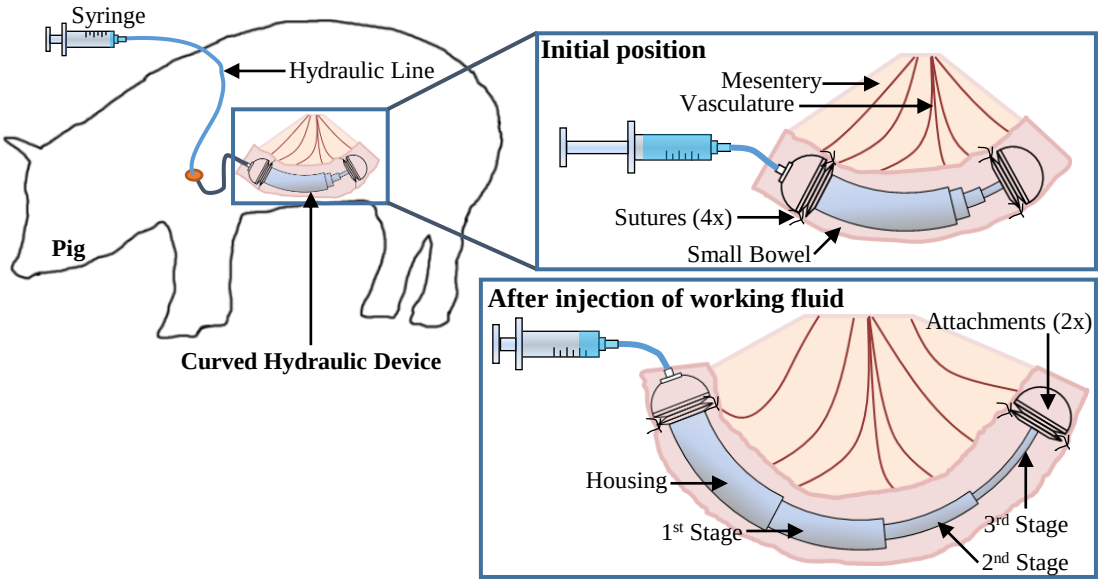

Figure 2.3. Architecture of Curved Hydraulic Device.
The architecture of the Curved Hydraulic Device is composed of a housing and three stages, which extend (as fluid is injected from an external syringe) to place tension on the tissue and induce mechanotransductive small bowel growth.

have similar nutritional requirements [10], similar digestive physiology [11], similar susceptibility to enteric pathogens [12], and they are an important model of natural GI tract growth in preterm infants [13]. The Curved Hydraulic Device is composed of an external syringe which is used to push the working fluid into a set of concentric telescoping curved cylinders equipped with seals. The largest cylinder, or housing (Figure 2.3), is fitted with a device-to-tissue attachment and a connection for the hydraulic line. Opposite the hydraulic line, another device-to-tissue attachment is fixed to the last (smallest diameter) stage. The extension of the curved hydraulic device is driven by the input of fluid from and external syringe through a transdermal hydraulic line. The device is initially collapsed when implanted. As the external syringe is depressed, the stages of the hydraulic device extend due to the conservation of the fluid volume provided by the seals. For a fixed input volume, the expansion of the device is not known because it depends on which stage or stages have extended. Tension on the small bowel tissue is applied by the device-to-tissue attachments which are sutured into the tissue, and through the process of mechanotransduction, the tissue grows, thus reducing tension. The process of loading the tissue and allowing time for growth is repeated at a regular interval for the duration of the one to three week implantation period.

The design of the Curved Hydraulic Device was dependent on and guided by the net expansion target. However, clinical tissue lengthening goals have not been previously set and must be determined based on the experience of pediatric surgeons in the care of SBS patients. The goal of the Curved Hydraulic Device *in vivo* studies is to generate large net growth and exceed previously achieved expansion factors of growth with clinically relevant models. To treat many cases of pediatric SBS with the mechanotransduction approach, where success is measured by the patient's ability to wean from TPN, greater net and expansion ratio growth of the small bowel is required than that produced in the Linear Hydraulic Device studies [1,2,14]. Recently, the remaining small bowel length after resection was found to be a poor predictor of a patient's ability to wean off of TPN, while the percentage of expected length, which changes rapidly in utero, was found to be a strong predictor [15]. In a retrospective study of 80 neonates, 83.1% of the patients' whose small bowel length was greater than or equal to 10% of their expected small bowel length were able to wean from TPN, while only 10.5% could do the same with less than 10% of their expected small bowel length. However, the percent of expected small bowel length varies widely from patient to patient following major resection, leading to a large range of required net increases, 1 cm to 25 cm (based on the study), to achieve greater than or equal to 10% of the expected small bowel length in neonates. To improve on the expansion capability of the Linear Hydraulic Device, the net expansion target was set to greater than 10 cm, whereas the Linear Hydraulic Device studies reported an average of 5.5 cm of net expansion in the first study [2] and 10.3 cm in the second [1]. To achieve greater net expansion and expansion ratio than the Linear Hydraulic Device, which had two stages, the Curved Hydraulic Device was designed with an additional third stage. The expansion ratio target of the device was set to at least 2X to improve on the capability of the Linear Hydraulic Device. Additionally, the Bianchi and STEP surgical small bowel lengthening procedures have reported expansion amounts in the range of 1.9 to 2X [16–18]. Although the device expansion target is 2X, because the attachments were designed to connect circumferentially rather than by end abutment, the *tissue* expansion ratio can be set much greater than 2X by modifying the initial position of the attachments relative to the housing of the device.

In addition to the goals for the net extension and expansion factor of the device, the geometric size constraints on the Curved Hydraulic Device were severely constrained by the peritoneal cavity length and bowel lumen diameter of the porcine models. To define these constraints, measurements

were made directly of porcine anatomy to determine the peritoneal cavity length, height of mesentery, and relaxed bowel diameter. The abdominal cavity length was measured to determine the maximum length of the device, defined as the greatest linear distance between the two ends of the device when fully extended. Radiographs of young (~6 months) porcine models from previous *in vivo* studies indicated that approximately 30 cm is the upper limit on the maximum length of the device. The mesenteric height is defined as the length of mesentery between the bowel and the superior mesenteric artery. This dimension is relevant for specifying the radius of curvature of the Curved Hydraulic Device to minimize mesenteric tension at the time of the implantation and during the expansion. Based on measurements taken during previous *in vivo* studies, a mesenteric height of 9 cm was found and thus set as the target for the radius of curvature of the Curved Hydraulic Device. To determine the maximum outer diameter of the intraluminally placed device, estimates of the bowel inner diameter were determined by removing short lengths of small bowel and cutting them into strips such that their circumference could be directly measured. Assuming the shape of the bowel to be circular, the inner diameter was found by dividing the circumference by π. Using this method, the relaxed inner bowel diameter of the porcine models (4 to 6 month old) was estimated at 1.7 cm.

The architecture of a Curved Hydraulic Device is unique, and the non-linear actuator has a range of other potential applications beyond studying enterogenesis in porcine models, such as enabling studies of esophageal or intestinal growth with differently sized animal models. The general design approach and considerations addressed herein serves as foundation for developing this class of actuators for other applications.

2.2. Curved Hydraulic Device Prototype

To enable the *in vivo* studies, a prototype of the Curved Hydraulic Device was designed and built as shown in Figure 2.4. The three main elements of the design are presented in the following section which include material selection based on biocompatibility and yield strength, the fabrication of the curved housing and stages, the sealing of the device, and the device-to-tissue attachments.

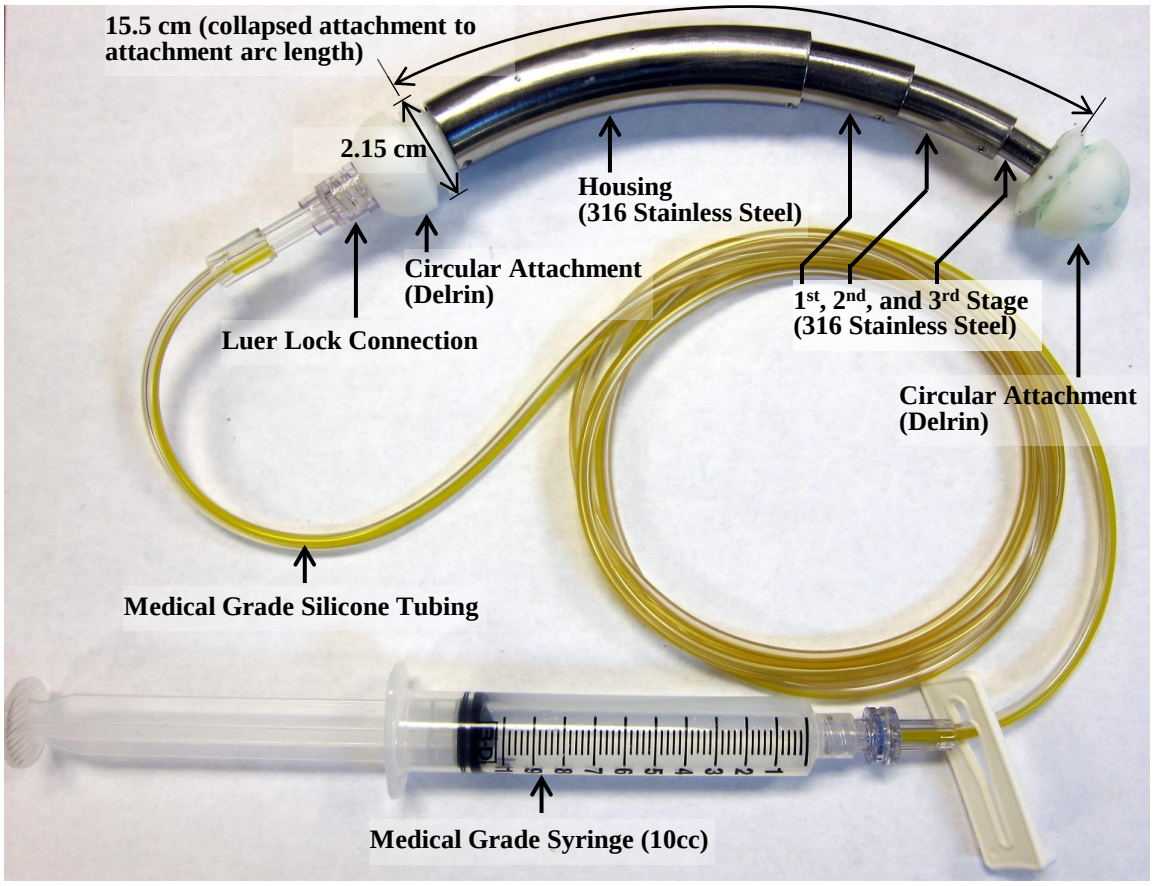

Figure 2.4. Prototype of Curved Hydraulic Device.

The Curved Hydraulic Device was composed of Delrin seals and attachments and 316 stainless steel housing and stages. The housing and stages were curved by manually bending the tubing around a mandrel. An external medical grade syringe was used to drive the working fluid into the device.

2.2.1. Curved Housing and Stages

The fabrication of the housing and stages was challenging because the chosen material had to be biocompatible, the housing and stages had to be curved with approximately identical radii of curvature, and the inner and outer diameters of the housing and stages had to be such that they fit concentrically while simultaneously fitting available seals. Custom made housing and stages from material suppliers were considered but disregarded due to their high cost and lengthy lead time compared to off-the-shelf options. Rapid prototyping the housing and stages was also considered, but was also disregarded due to limitations on material choice. Specifically, the SLA method uses epoxy resins that can lose dimensional stability in fluids, and while the FDM method uses more

robust materials like ABS, the resolution of parts created with this technique is not conducive to make sliding and sealable components.

Using the CES Selector software package (Granta Design), biocompatible materials were identified for the housing and stages to prevent health complications during implantations and to protect the Curved Hydraulic Device from the *in vivo* environment. Two material choices were specified for further down-selection: 316 stainless steel, and Delrin 150, a biocompatible [19] thermoplastic polymer that is readily available and easily machinable.

To form the curved cylinders, stainless steel may be cold formed, and Delrin, which is a thermoplastic, may be formed at high temperature. To choose between the materials, an FEA analysis of the housing and three stages was performed for stainless steel 316 and Delrin using a set of dimensions from an initial design for the length, inner diameter, and thickness of the material for the housing and each stage. To develop a conservative design, an assumed end load of 15 lbf (6.8 kgf) was applied at 45 degrees relative to the faces of each stage while the opposite face was rigidly fixed. The magnitude of the assumed end load was not specified based on the expected applied tensile loading on the distracted bowel segment. Rather, it was chosen based on the possibility that the weight of the animal could apply a bending moment to the extended device or that adhesions connecting the distracted segment to the peritoneal wall could transfer large loads to the device. The initial design (inner and outer diameters) of the housing and stages was based on matching commercially available stainless steel tubing with compatible O-Ring seals while keeping the outer diameter of the housing less than 1.7 cm to fit within the small bowel.

Results from the numerical study are shown in Table 2.1. As expected, the stainless steel components had higher safety factors against yielding than the Delrin components. The simulations for the second and third Delrin stages did not complete due to post-yield numerical instabilities arising from large displacement. However, the first Delrin stage yielded during the simulation. Therefore, stainless steel was the chosen housing and stage material for the Curved Hydraulic Device prototype. Because none of the stainless steel components yielded in the FEA analysis, the initial housing and stages were not redesigned.

Table 2.1. FEA Results of Stainless Steel and Delrin Tubing for Curved Hydraulic Device
FEA results showed that the original design of the Curved Hydraulic Device will not yield if made with 316 stainless steel. If made of Delrin, all stages of the model yield. The 2nd and 3rd stages of the Delrin model failed due to numerical instabilities arising from large displacement secondary to yielding.

Material	Component	Max Stress (Mpa)	Safety Factor
Stainless Steel	Housing	18	9.44
(Yield Stress: 170 MPa)	1st Stage	63	2.7
	2nd Stage	143	1.19
	3rd Stage	102	1.67
Delrin	Housing	20	3.15
(Yield Stress: 63 MPa)	1st Stage	66	0.95
	2nd Stage	Fail- N/A	Fail- N/A
	3rd Stage	Fail- N/A	Fail- N/A

Dimensions for the housing and three stages are shown in Table 2.2. The curvature of the stainless steel tubes was developed by manually bending them around a mandrel with a diameter of 9 cm to match the radius of bowel curvature measured in porcine models. To prevent kinks in the tubes while bending, wet sand was compacted inside the tubing and the ends were sealed. The wet sand packed tubes were fixed tightly between a clamp and a mandrel, and the free end of the tube was manually pulled around the mandrel until it conformed to the desired radius. Due to the tubing springing back in the absence of the applied external load, the actual radius of curvature increased to approximately 10.6 cm. The less compliant stages had a greater spring-back effect and thus required mandrels with less than a 9 cm diameter for bending. Bending the tubing in this manner also introduced an ellipticity into the cross-section that made the minor and major

Table 2.2. Dimension of Housing and Three Stages of Curved Hydraulic Device.
The dimensions of the original Curved Hydraulic Device are shown. The design was based on keeping the outer diameter of the housing less than 1.7 cm to fit within the bowel lumen, while finding commercially available 316 stainless steel tubing with compatible dimensions for use with standard O-rings.

Component	Outer Diameter		Inner Diameter	
	(in)	(cm)	(in)	(cm)
Housing	0.625	1.588	0.555	1.41
1st Stage	0.5	1.27	0.43	1.092
2nd Stage	0.375	0.953	0.305	0.775
3rd Stage	0.25	0.635	N/A (Solid Rod)	

diameters vary on the order of ten to fifteen thousands of an inch. This ellipticity made the design of the seal and seal mounts challenging.

2.2.2. Sealing

The ellipticity of the housing and stages made sealing a challenge, because radial gland seals are designed for circular cross-sections and the curved cylinders were slightly elliptical. Instead of using traditional O-Ring seals, the sealing of Curved Hydraulic Device was achieved with a series of six seals taken from medical grade syringes. Compared to traditional O-Ring seals, the butyl rubber syringe seals conformed more securely to the slightly elliptical cross-section of the stainless steel tubing. As shown in Figure 2.5, two 10 cc syringe seals were used to seal between the proximal attachment/housing interface and the housing/1st stage interface. Two 5 cc syringe seals were used between the seal holder/1st stage interface and the 1st/2nd stage interface, and two 3 cc

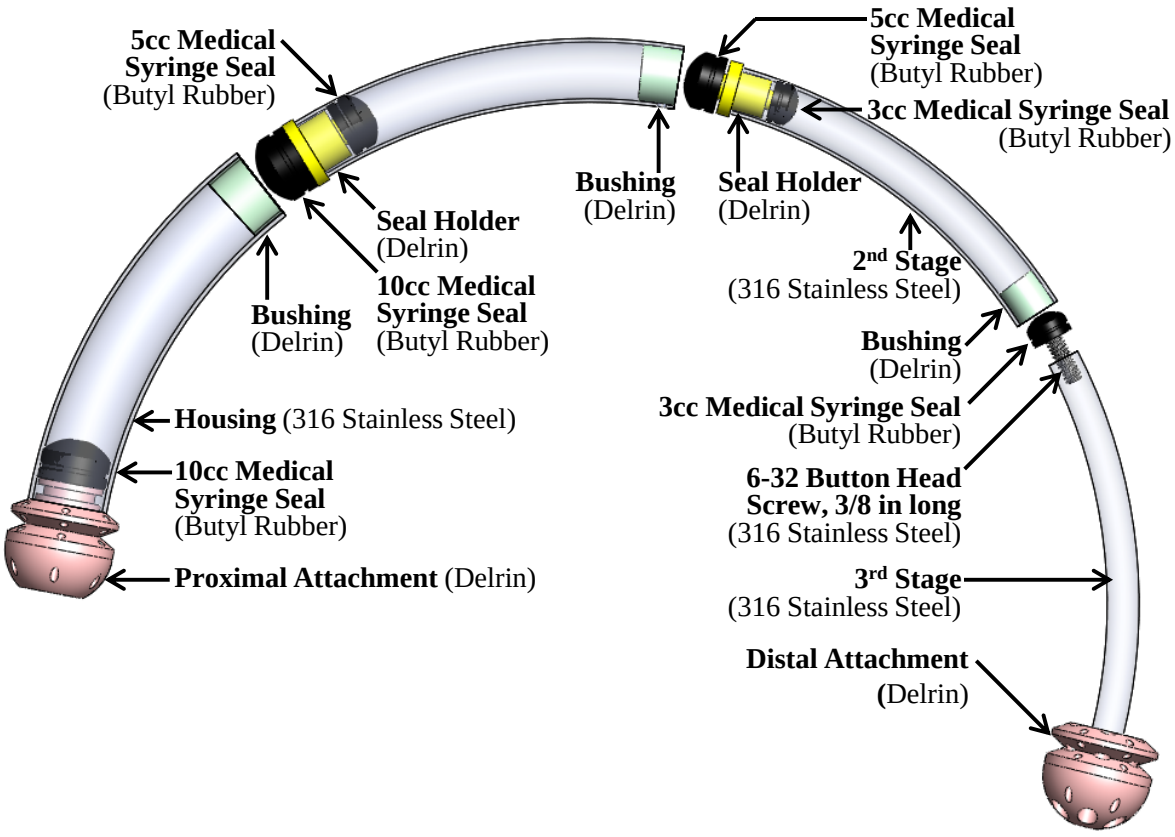

Figure 2.5. Exploded Schematic View of the Curved Hydraulic Device.
The assembly and materials or the Curved Hydraulic Device are shown. Overlapping components were fixed together by epoxy (bushing/housing, bushings/stages), set screws (proximal attachment/housing, seal holders/stages), and with mounts (seals/seal holders). The distal attachment screws onto the final stage.

syringe seals were used between the seal holder/2nd stage interface and the 2nd/3rd stage interface. The seals were held in place by two seal holders machined from Delrin and one stainless steel 6-32 button head screw fixed to the third stage. To prevent the complete separation of the stages and housing during operation, the seal holders and 6-32 screw interfere with the three approximately 0.020 inch thick Delrin bearings fixed to the end of housing, the first stage, and the second stage by stainless steel 2-56 set screws. The bearings, seals, seal holders, and 6-32 button head screw are shown in an exploded schematic view of the Curved Hydraulic Device in Figure 2.5.

2.2.3. Attachment to Tissue

The safe and reliable transfer of load from the device to the small bowel is possibly one of the greatest challenges to demonstrating the clinical potential of mechanotransductive tissue growth. There are safety issues related to ischemia (reduced blood flow) and tearing of the bowel. There are also practical issues; the bowel lumen is smooth, slippery, and lined with a mucosal layer which continuously and naturally sloughs away. Prior enterogenesis devices have successfully transferred load to isolated segments of bowel with a single surgical closed end, like the external screw, or with both ends closed, like the Intraluminal Spring [7–9] and the linear hydraulic device [1]. However this attachment method, which will be referred to as end abutment, is clinically very undesirable because significantly long segments of bowel are lost in the process of creating multiple anastomoses and restoring the distracted segment back into the continuity of the GI tract. Furthermore, in a study where both ends of the isolated segment were surgically closed, the buildup of mucous within the segment proved to be a lethal complication [14]. To overcome this complication, transdermal drainage catheters were placed in the isolated segment in subsequent experiments, but they had to be flushed regularly to prevent clogging, and they increased the risk of infection and bowel leakage.

To transfer load from the Curved Hydraulic Device to the segment of bowel in which it is implanted, two Delrin attachments are fixed on the opposing ends of the device. Rather than the end abutment attachment method, the attachments transferred load through rings of sutures to the bowel wall. The attachments supported six evenly placed sutures each, and were filleted to prevent ischemic injury to the bowel wall. Designing the number of holes for the sutures was not trivial; too many holes would lead to bowel tearing (like perforated paper), but too few holes would lead to higher loads applied to the tissue by each suture. Based on these considerations and some brief

ex vivo evaluations of prototyped attachments, the choice of six holes was made, which placed each suture approximately 1 cm apart along the circumference of the bowel lumen. The innermost layer of the bowel, or mucosa, produces mucous and continuously sloughs off cells. To prevent the buildup the mucous and other enteral contents between the attachments, the distal, or downstream, attachment was machined to have six 0.16 inch diameter holes. The hole size was chosen by maximizing the diameter without comprising the structural integrity of the attachment, although no formal design optimization technique was applied. Based on a prior experimental study [20] that explored the minimum flow-through area to allow the safe passage of enteral contents, the six 0.16 diameter provide more than enough flow-through area. Thus, the need for drainage catheters was eliminated. The proximal, or upstream, attachment was fitted with a female luer lock adaptor to connect the medical grade silicone hydraulic line.

2.3. Validation and Characterization

To prepare for *in vivo* experiments, the Curved Hydraulic Device performance was evaluated on the benchtop. Experiments were performed to detect if there were leaks, to evaluate the force output, and to measure the relationship between the input fluid volume and the displacement of the three devices stages. To detect leaks, the displacement of the stages was blocked with the device collapsed as well as with the device fully extended, and fluid pressure within the device was elevated by manually attempting to force fluid through the hydraulic line with an external syringe. For both the collapsed and extended configurations, the seals of the Curved Hydraulic Device held with minimal (less than approximately 5% of the full expansion volume) leakage. To evaluate the force output, the Curved Hydraulic Device was successfully extended against an external load of 1kg. The performance of the Curved Hydraulic Device was characterized by measuring the device expansion versus volume of injected water to determine fluid injection rates during *in vivo* experiments, where the motion of the device cannot be monitored save for the use of radiographs. To collect the data shown the Figure 2.6, the displacement arc length was measured with a ruler for even increments of injected water volume. Because the housing, 1st stage, and 2nd stage have different inner diameters, they expand at different rates with respect to the volume of injected water. The first stage (largest) displaces 0.8 cm/ml, the second stage displaces 1.0 cm/ml, and third stage (smallest) displaces 1.8 cm/ml of inputted volume. Additionally, the order in which the stages extended varied between trials and was therefore an unknown during implantation. Thus,

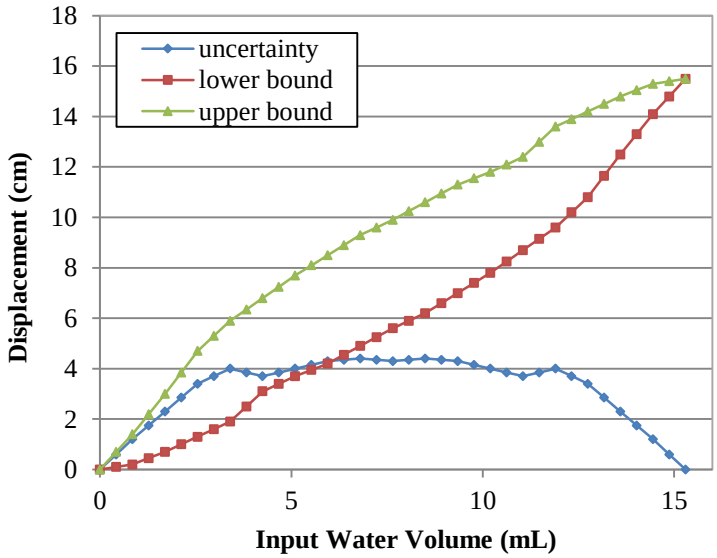

Figure 2.6. Curved Hydraulic Device Displacement Versus Input Volume.
The upper bound, lower bound, and the uncertainty (upper minus lower bound) of the Curved Hydraulic Device displacement is shown. The uncertainty arises because each stage of the device extends a different amount per fixed fluid injection and the order in which the stages extend was not repeatable.

Figure 2.6 shows the lower displacement bound, were the stages extend one at a time in ascending order: 1st, 2nd, and then 3rd. If the stages extend one at a time in descending order, the expansion of the devices follows upper displacement bound. While implanted, the total displacement of the device may vary as much as the difference of the upper and lower bound, giving a maximum uncertainty of approximately 4.5 cm at half the total volume capacity of the device (assuming no hydraulic fluid has leaked). If no hydraulic fluid has leaked, this uncertainty in the device displacement goes to zero as the inputted volume reaches full capacity. This variation is problematic for studies where the effect of displacement rate on growth characteristics is sought, and it may also be too unsafe for clinical applications, but this result is suitable for the large growth and expansion ratio goals of this chapter. The final displacement and inputted volume are 15.5 cm and 15.3 mL, respectively, giving the Curved Hydraulic Device an average displacement per volume rate of 1.01 cm/mL and an extension ratio of 2.1X.

2.4. *In Vivo* Experimental Studies

To demonstrate the feasibility and potential of the mechanotransductive approach to treating short bowel syndrome, a series of medical experiments were completed that used the expansion

capabilities of the Curved Hydraulic Device. The goal of the series of experiments was to evaluate the feasibility and potential of the mechanotransductive approach to correcting SBS by investigating the potential for inducing large net growth, large expansion factor growth, and observing the mesentery supporting the distracted segment for an increase in vascularity. To promote large net growth, the Curved Hydraulic Device was implanted intraluminally in porcine animal models and extended by impulsively increasing the displacement of the hydraulic device twice daily over the course of approximately two weeks. To distinguish between actual growth and the permanent deformation of the tissue, samples of the grown tissue were compared with controls to determine if there were morphological differences, increased proliferation of cells, preserved barrier function, and to evaluate adaptation of the mesenteric vasculature.

2.4.1. Experimental Procedure

Three procedures have been developed to guide the experimental studies: the surgical implantation procedure, the device expansion protocol during the distraction period, and the surgical device removal and post experiment tissue analysis plan. All animal experiments were conducted at the University of Michigan with approval from the University Committee on the Use and Care of Animals (protocol number 09026).

A surgical implantation procedure was developed to implant the Curved Hydraulic Device intraluminally, but not within the continuous GI tract. Rather, the device was implanted within a Roux limb connecting the continuous GI tract to a stoma located on the underside of the porcine model. The surgery began with a 15 cm midline incision to open the abdominal cavity of the porcine model. The small bowel was manipulated to determine the flow direction of enteral contents and to locate the Ligament of Treitz, which marks the start of the small intestine. Approximately 60 cm along the length of small bowel from the Ligament of Treitz the small bowel was cut, creating two open ends of bowel labeled (a) and (b), as shown in Figure 2.7. Approximately 60 to 75 cm along the length of bowel from (b), an end-to-side anastomosis was created, connecting (a) to (c) and restoring the continuity of the GI tract. The segment of small bowel from (b) to (c), or Roux limb, was no longer in the continuity of the GI tract and would not pass ingested contents, however, the health of the Roux limb was maintained by the blood supply from the intact mesentery. During the creation of the Roux limb, the Curved Hydraulic Device was sterilized by soaking it in a liquid sterilant (Metrix, Metricide®) for the manufacturer recommend

time of 40 minutes. After sterilization, the device was thoroughly rinsed with sterile saline to prevent any sterilant from getting into the surgical field. The Curved Hydraulic Device was inserted, 3rd stage end first, into the open end of the Roux limb, and was sutured in place with the device-to-tissue attachments. Laser Doppler images, which captured the rate of blood flow, of the bowel and mesentery were acquired to confirm the absence of device-induced ischemia. A stoma, or surgically created opening, was made in the skin and fascia of the abdomen, and the Roux limb was secured to the stoma at the fascia and skin. The final steps of the surgery were to route the hydraulic line through the Roux limb, connect the external injection syringe to the hydraulic line, and secure the external injection syringe and hydraulic line to the center of the porcine model's back.

The planned length of the implantations was approximately two weeks long, during which the full expansion is device was evenly distributed (as much as possible) by injecting the same amount of working fluid each day. Two injections of fluid, approximately 0.6 ml each, were given each day – one in the morning, and one in the evening. At the time of each injection, the health of the pig was observed and recorded. To monitor the displacement progress of the device, radiographs were taken during some experiments.

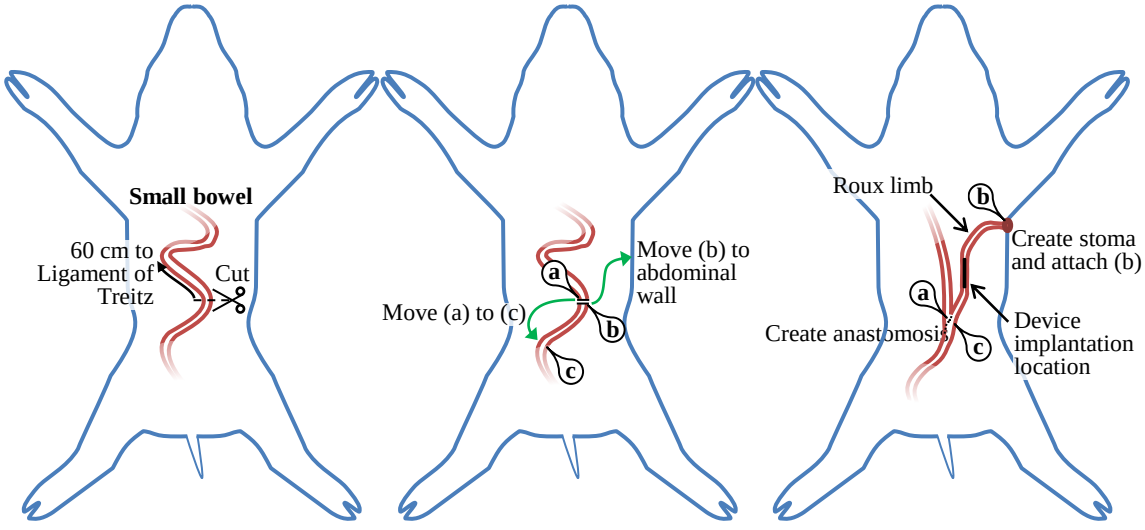

Figure 2.7. Schematic of Surgical Implantation Procedure.
The Curved Hydraulic Device was implanted in a Roux limb created by cutting the small bowel and creating two open ends, (a) and (b), creating an anastomosis at (a) and (c), and connecting (b) to a stoma on the abdomen of the porcine model.

At the device removal and tissue harvest surgery, tissue samples were taken from the non-distracted Roux Limb as the control samples, from the distracted Roux limb, and from normal small bowel for comparison. During the distraction period, the Roux limb is not exposed to what the animal models ingest, except for cases of reflux into the Roux limb. The lack of nutrient rich contents flowing though the lumen of the Roux limb has an effect on its physiology, making the non-distracted Roux limb tissue sample the most appropriate control for evaluating the distracted tissue segment. The analyses for evaluating the tissue health and function included evaluating the barrier function by measuring the tissue's transepithelial electrical resistance, evaluating growth by counting the percentage of proliferating cells marked by PCNA, and examining the general health by observing the tissue morphology from histologic slides. The extent of vasculature adaptation within the mesentery supporting the distracted segment was also captured by taking high resolution photographs, and by injecting a radiopaque dye (Microfil® injection compound) into the vasculature, taking CT scans of the tissue, and creating three-dimensional reconstructions.

2.4.2. *In Vivo* Results and Discussion

Four trials have been successfully conducted over the course of several years with the Curved Hydraulic Device. Reliable attachment to the bowel wall has proven to be challenging. However, strong results concerning tissue growth, mesenteric adaptation, and important design insights for clinically-relevant enterogenesis devices have been achieved.

2.4.2.1. Tissue Growth

The growth of healthy porcine small bowel tissue has been successfully induced by the application of distractive loads with the Curved Hydraulic Device in a series of four experiments as shown in Table 2.3. The amount of net tissue growth was in the range of 4.9 cm to 8.9 cm, while the ratio of tissue expansion varied from 1.6 to 2.2X. Many other experiments with the Curved Hydraulic Device were conducted than what is presented here, but due to challenges related to the poor reliability of tissue attachment sutures and tissue marking sutures, the amount of tissue length grown could only be determined for the four experiments presented here.

Table 2.3. Tissue Growth Results with Curved Hydraulic Device

Net tissue lengthening and expansion ratios of tissue growth ranged from 5.4 to 8.9 cm and 1.6 to 2.2X, respectively. Variation in the initial segment length was achieved by changing the mounting locations of the tissue attachments.

Trial	Experiment Explant Date	Initial Segment Length (cm)	Net Tissue Lengthening (cm)	Expansion Ratio of Tissue
1	12/21/2011	15.0	8.9	1.6
2	6/13/2012	13.2	7.5	1.6
3	2/19/2013	4.5	4.9	2.1
4	4/26/2013	4.5	5.4	2.2

To investigate if the grown tissue was as healthy and functionally similar to normal small bowel, the transepithelial electrical resistance (TER) of the tissue was measured, the percentage of proliferation cells was determined, and the morphology of the tissue was observed with histologic slides.

2.4.2.1.1. Transepithelial Electrical Resistance

Small bowel tissue transports nutrients across the epithelium while simultaneously maintaining a barrier that prevents the passage of harmful bacteria, viruses, and organisms. One method to measure the strength of the tissue barrier function is to evaluate the TER using a Ussing Chamber. Measurements of TER were taken for the Curved Hydraulic Device experiment ending in December of 2011. Tissue samples were taken from the normal fed bowel, the unfed Roux limb control, and two sections of the distracted tissue segment labeled device middle and device end (Figure 2.8). The results suggested that, relative to the Roux Y Control, the TER of the distracted tissue segments was preserved. This is a positive indicator that true small bowel growth occurred without resulting in microscopic tearing or perforations. If the small bowel was stretched or permanently deformed rather than grown, the expected TER would be significantly lower than the Roux limb control segment, which was not the case. If a microscopic tear or perforation of the tissue was present, the measured TER would decrease to near zero because there would be no tissue to prevent the flow of ions across the Ussing Chamber.

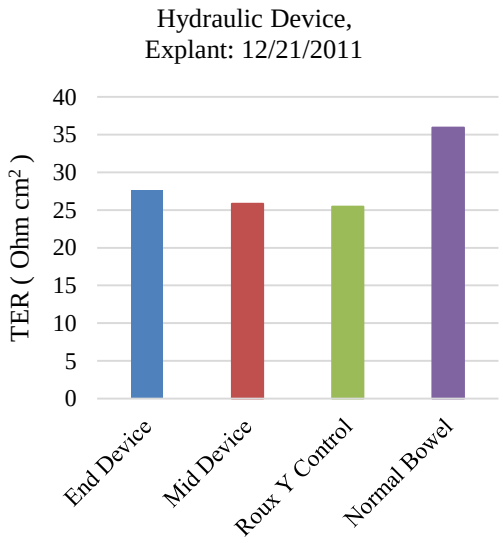

Figure 2.8. Transepithelial Electrical Resistance of Small Bowel Samples. Compared to the Roux Y Control, tissue samples from the end and middle of the device did not have significantly different transepithelial electrical resistance. This result suggests that the grown bowel tissue was not perforated on a microscopic level and that the barrier function of the grown tissue segment was maintained.

2.4.2.1.2. Cell Proliferation

The small bowel has a high turnover rate of cells that form in the crypt villus complex and subsequently slough off into the bowel lumen. If small bowel growth is occurring, the rate at which cells are proliferating should be at least greater than that of tissue that is not growing. To measure the percentage of proliferating cells, tissue samples were stained to test for the presence of Proliferating Cell Nuclear Antigen, or PCNA. The percentage of proliferating, or PCNA positive, cells were measured for all of the experiments except for the one ending on 12/21/2011, where the histology could not be used due to difficulties associated with slide preparation. Similarly, the data from the "Normal Bowel" for the experiment ending on 4/26/2013 could not be used. Otherwise, PCNA data were taken from normal (or fed) bowel, the roux limb control, and two sections of the distracted tissue segment. The plotted data indicate the average ratio of proliferating cells to all cells counted along each crypt/villus complex per high power field.

The results (Figure 2.9) show that across all samples, the range of proliferating cells is in the range of approximately 30 to 70 percent of the total cells. The data for the distracted portion (End Device and Mid Device) are compared most accurately with the Roux Y Control for several reasons. First, like the Roux Y Control, the End Device and Mid Device tissue samples were not

exposed to enteral contents during the two week experimentation period, whereas the Normal Bowel was in the continuous GI tract and exposed to enteral contents. The lack of enteral content exposure may lead to disuse atrophy in the tissue and other physiological changes. Thus, the Normal Bowel samples are not appropriate controls. Secondly, the tissue for the End Device, Mid Device, and Roux Y Control are all surgically manipulated at the implantation surgery, unlike the Normal Bowel. The surgical manipulation of the tissue may lead to physiological changes, again making the Roux Y Control more appropriate.

There were statistically significant results for the experiments ending on 6/13/12 and 4/26/2013, where the percentage of proliferation cells on the End Device and Mid Device were

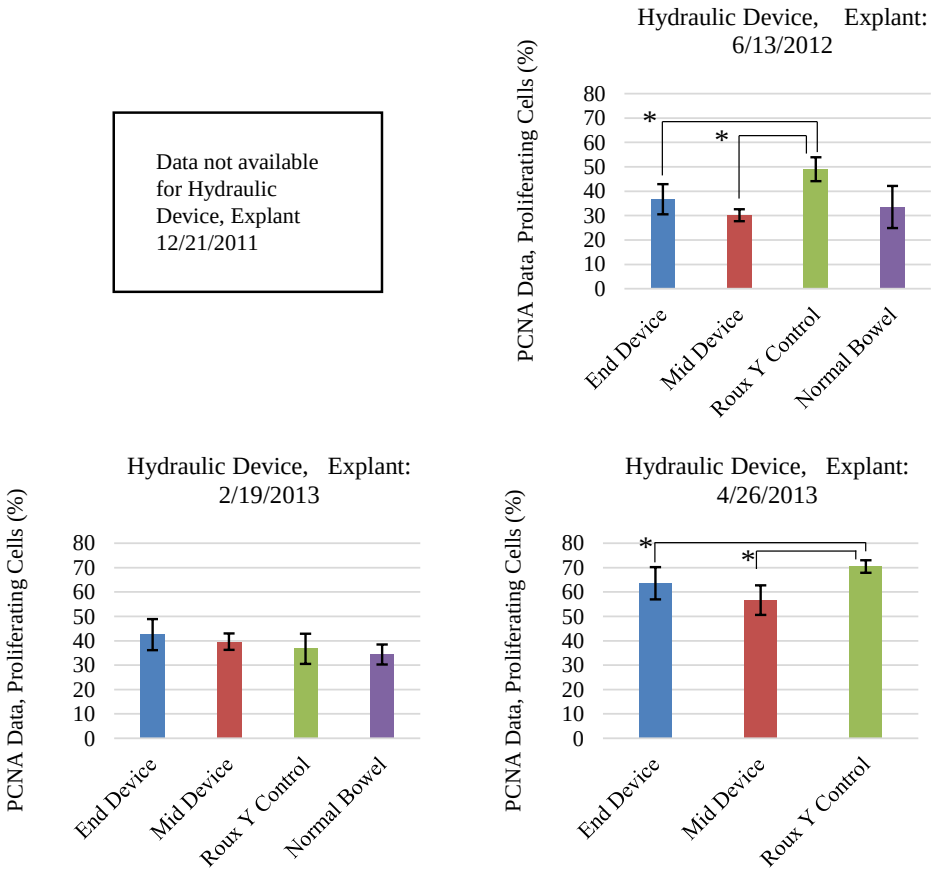

Figure 2.9. Percentage of Proliferating Cells in Small Bowel Samples.
Relative to the Roux limb control, the percentage of proliferating cells decreased in the End and Mid Device for the experiments ending on 6/13/2012 and 4/26/2013. However, the medical significance of this result is minimal, as the overall maintenance of cell proliferation was observed across trials, and the End and Mid Device were not significantly different from the Normal Bowel in the experiment ending on 6/13/2012. This result indicates that true bowel growth was induced. Pairwise t-Tests were taken only for End Device against the Roux Y Control, and the Mid Device against the Roux Y Control. *Brackets indicate statistically significant differences ($p < 0.05$).

less than that of the Roux Y Control (t-test: two-sample assuming unequal variances, $p < 0.05$). Although the results are mathematically significant, the medical significance of these results is not necessarily important. Especially considering that there was no statistically significant difference between the Normal Bowel and the distracted segments for the experiment ending on 6/13/2012. Although the percentage of proliferating cells was less than the Roux Y Control in two of the experiments, the percentage of proliferating cells was not low enough to cause concern. For the experiment ending on 2/19/2013, there were no statistically significant differences found for any pairing of tissue sample locations. The results suggest that inducing small bowel growth by the application of tension does not lead to medically significant changes in the percentage of proliferating cells in the epithelium. However, the importance of timing the fixation of the tissue for histology was not explored. Because of the high turnover rate of cells in the epithelium [21], the captured change of the rate of cell proliferation secondary to applied tissue tension may be highly dependent on how quickly the tissue can be fixated after distraction. Nonetheless, the results presented here do not suggest any negative health effect on tissue as a result of the applied load. The general maintenance of cell proliferation also indicates that actual bowel growth occurred, rather than stretching.

2.4.2.1.3. Morphology

The morphology of the small bowel tissue was also observed to determine the health of the tissue. In the distracted tissue segments, there was no evidence of gross tearing, minimal disruption of the mucosa, and minimal swelling of the tissue, which indicated that the distraction process did not physically harm the tissue. The lack of mucosal disruption further strengthens the result that the TER of the distracted segment was maintained. Relevant morphologic features of the tissue, which included crypt depth, villus height, and muscle layer thickness were measured.

Results for the total muscle thickness (longitudinal muscle thickness plus circular muscle thickness) are shown in Figure 2.10. For all experiments excluding the one ending on 4/26/2013, the total muscle thickness for the End Device and Mid Device were greater than that of the Roux Y Control with statistical significance (t-test: two-sample assuming unequal variances, $p < 0.05$). The increase of muscle layer thickness was largely attributed to hypertrophy, an enlargement of cell size, rather than hyperplasia, an increase in the number of cells. Although the medical significance of this result is not clear, increased muscle layer thickness due to hypertrophy has been observed in all but one prior study of enterogenesis [3,4,6–9,22], as indicated by Table 1.4 in Chapter One concerning the statistically significant medical results of rabbit and rat enterogenesis

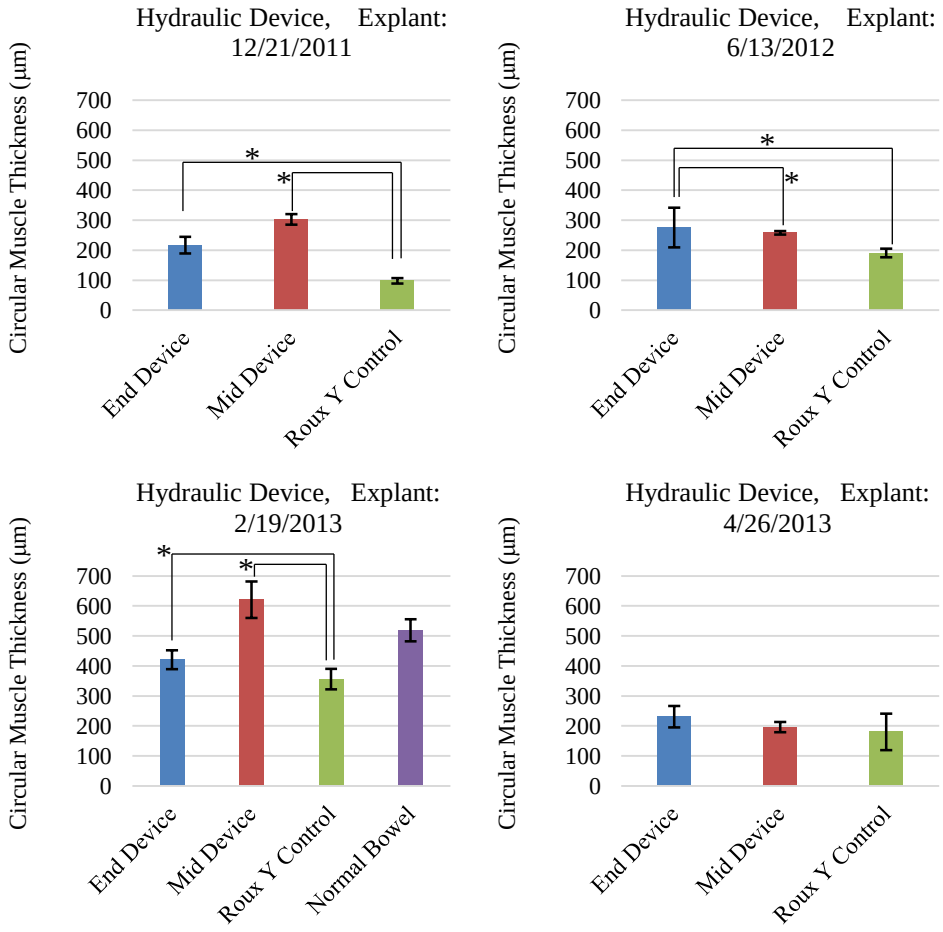

Figure 2.10. Total Muscle Height.

Relative to the Roux limb control, statistically significant increases in the Circular Muscle Thickness were measured for the experiments ending on 12/21/2011, 6/13/2012, and 2/19/2013. Pairwise t-Tests were taken only for End Device against Roux Y Control, and Mid Device against Roux Y Control. *Brackets indicate statistically significant differences ($p < 0.05$)

studies. In the single study that did not report muscle layer thickening [23], fluidic pressure was applied to segments of rat small bowel rather than device-enabled pure tension.

The villus height and crypt depth were also measured, and ranged from 100 to 350 μm for the villus height, and from 150 to 350 μm for the crypt depth. Unlike muscle layer thickness, both the villus height and crypt depth were not significantly different compared to the Roux Y Control and Normal Bowel (t-test: two-sample assuming unequal variances, $p < 0.05$). The preservation of these structures is important to the maintenance of tissue health and function. A reduction of villus height greatly decreases the absorptive surface area, and crypt depth is related to the rate at which new epithelial cells are formed and their absorptive capacity [24]. Thus, the measured lack of change in these structure was a positive indication of health bowel growth.

Taken together, the medical analyses of the tissue samples strongly suggested that the true growth of healthy and functional small bowel can be induced the by application of distractive loading. However, to support greater lengths of small bowel tissue, the vasculature of the mesentery must adapt to continue distributing blood to the tissue.

2.4.2.2. Vascular Adaptation

The adaptation of the mesenteric vasculature has been successfully observed, suggesting the long-term health of distracted tissue segments will be sustained [25]. Figure 2.11 shows two high resolution photographs of the mesentery before (left) and after (right) tissue distraction. The images illustrate how the vasculature of the mesentery adapts by neovascularization, the formation of small blood vessels branching off of the main vessels. Qualitatively, the figure shows that the density of blood vessels is increased in the distracted segment. To quantify these results, a novel method for measuring the volume of blood vessels within samples of porcine mesentery was developed wherein a radiopaque agent (Microfil ®) is injected into the arterial vessels of the mesentery, the mesentery is then scanned using the CT imaging technique, and three-dimensional reconstructions are created by and analyzed with GE Healthcare's Microviewer software. The resulting three-dimensional reconstructions are shown in Figure 2.12. Approximately, a four-fold increase of neovascularization occurred in the mesentery supporting the distracted segment compared to the control. Thus, not only can healthy and functional small bowel growth be induced,

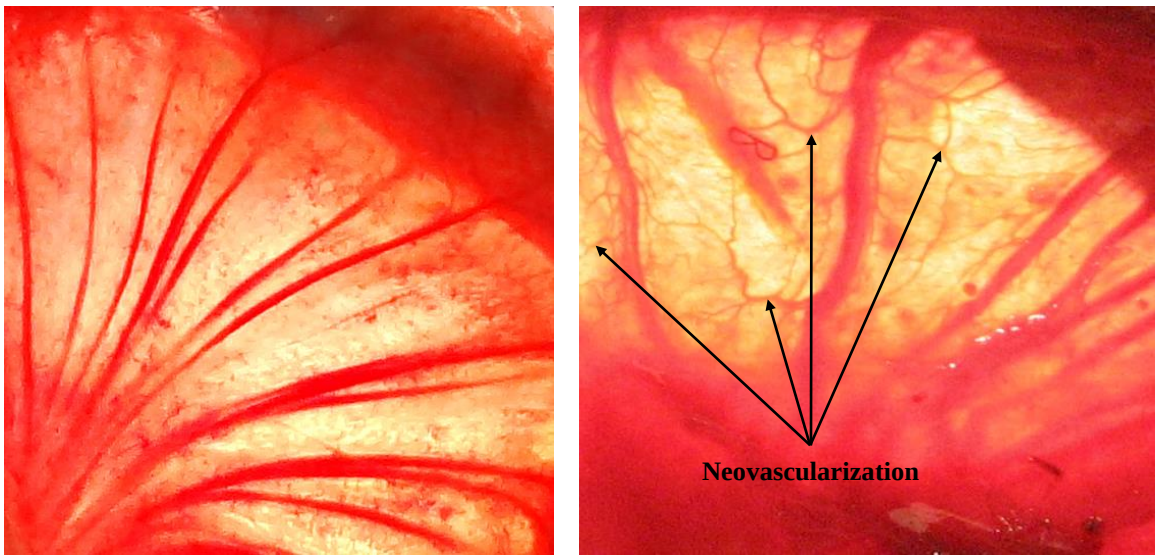

Figure 2.11. Mesentery of Distracted Segment at Implant (left) and Explant (right).
High resolution photographs showing the increase in mesenteric neovascularization. The increase is best observed by comparing the extent of small vessel growth between the major blood vessels.

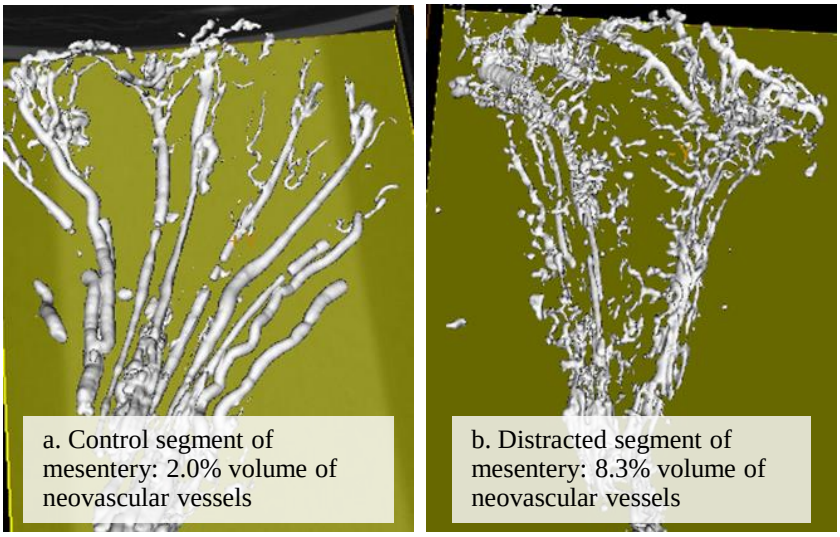

Figure 2.12. 3D Reconstructions of Control and Distracted Mesentery Samples.
Three-dimensional reconstructions were created by injecting a contrast agent into the blood vessels of the mesentery and taking CT scans of the tissue. This allowed the extent of neovascularization to be quantified. A 4X increase in neovascularization was measured, suggesting the sustainability of the grown bowel segment by increased blood perfusion within the tissue.

but the supporting mesentery adapts to supply the greater lengths of tissue by creating small arterial vessels to redistribute oxygen rich blood to the tissue.

2.4.2.3. Challenge of Tissue Attachment

Attaching reliably to the small intestine to transfer loads from the Curved Hydraulic Device has proven very difficult. At the device removal surgeries of several trials, the sutures connecting the circular attachments to the small bowel could not initially been found on the outside of the bowel. However, the sutures were still tied to the holes of the circular attachment. Unfortunately, they unexpectedly slipped through the full thickness of the small bowel tissue and could no longer transfer load from the device. Interestingly, the sutures' passage through the tissue did not cause enteral content leakage, because it appeared that the tissue healed around the sutures during the process. The lack of peritonitis provided further evidence that bowel leakage did not occur. To reinforce the attachments in the later trials, the sutures were reinforced with thick pieces of Strattice (denatured pig skin) or Alloderm (denatured human skin). Although the reinforcements improved the reliability of the tissue attachments, the material has also traveled through the bowel wall when the combination of applied bowel tension and the length of implantation were too great in several trials. Despite this challenge, very promising small growth and mesenteric adaptation results have been achieved with the Curved Hydraulic Device.

2.5. Conclusion

Short bowel syndrome treatments continue to suffer from high cost, lethal complications, and low rates of long-term success. To investigate the feasibility and potential of a new treatment approach based on mechanotransductive enterogenesis in clinically relevant animal models, the Curved Hydraulic Device was created and developed to enable experimental *in vivo* bowel growth studies with porcine animal models.

The Curved Hydraulic Device is a unique telescoping, three-stage, curvilinear hydraulic actuator which can be scaled for potential wide ranging applications. To design the device, measurements of the porcine small bowel diameter, mesenteric height, and length of the peritoneal cavity were made. The targeted expansion ratio of the device was set to 2X, which is similar to the expansion ratios achieved by the Bianchi and STEP procedures for surgically lengthening small bowel. The fabricated prototype had an expansion ratio of 2.1X and an expansion capacity of 15.5 cm, as determined by an experimental benchtop characterization of the device.

A series of four *in vivo* enterogenesis experiments with porcine animal models have successfully demonstrated healthy small bowel growth and have shown that the vasculature within the mesentery adapts to support the bowel as it grows. To quantify the adaptation of mesenteric vasculature, a method of visualizing the vasculature and determining the volume of blood vessels within the tissue was developed for porcine mesentery. Furthermore, insights have been made toward solving the general surgical challenge of reliably securing sutures under tension to soft tubular tissues like the esophagus and small intestine. Despite challenges related to the attachment of the device to the small bowel tissue, these studies have established the clinical relevance of the mechanotransductive approach to correcting short bowel syndrome and support further research into mechanotransductive enterogenesis.

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CHAPTER THREE. TREATMENT DEVELOPMENT STUDIES WITH AN INSTRUMENTED AND DISPLACEMENT CONTROLLED SMA DRIVEN RATCHETING DEVICE

Several important advantages of researching beyond feasibility have motivated a more detailed study of mechanotransductive small bowel growth. One important advantage of developing a better understanding of mechanotransductive bowel growth is exploration of the upper limit on how quickly small bowel can safely grow, which clinically leads to shorter implantations, reduced risk of complications such as bowel injury, obstruction, and bacterial overgrowth, and reduced costs. Furthermore, understanding limits on the maximum safe load and the nature of the small bowel tension over the length of an implantation can lead to better informed decisions of the expansion regimen of the future clinically oriented device.

Currently, the only enterogenesis device designed for porcine models are the Linear [1–3] and Curved Hydraulic Devices. Although these devices could be instrumented for monitoring the applied tension, they cannot fundamentally be used for repeatable displacement control because of the stick/slip nature of their expansion, uncertainty of the stage extension order, and the compliance of their hydraulic lines. Prior enterogenesis devices used in the rat and rabbit studies cannot be scaled up to enable these studies with porcine models due to practical safety concerns. The external [4] and internal screw devices [5] are not fully implantable and have rigid extracorporeal features that pose health risks for more active and larger animal models. The intraluminal spring [6–8] is fully implantable, but its use in porcine models poses risks as well due

to the requirement of draining the isolated bowel growth segment of mucous and the uncontrolled nature of the spring's expansion.

The objectives of this chapter are to enable and conduct bowel growth studies that explore the upper limit of safely applied tensile loads, explore the upper limit on how quickly small bowel tissue can be grown, and compare different strategies for expanding the tissue, such as applying a constant displacement rate, maintaining constant tension, and applying other displacement or force based profiles. To achieve these objectives in porcine models, an enterogenesis device with force instrumentation, displacement monitoring, and repeatable displacement control is needed. It is necessary to also have a wireless communication link to eliminate the need to tether the porcine models to a data acquisition system with electrical wires, because the porcine models would very likely injure themselves or the wired connection.

To enable more rigorous small bowel growth experiments, a fully implantable, wirelessly controlled, force sensing, and displacement sensing enterogenesis device with a Shape Memory Alloy (SMA) driven ratcheting mechanism (for reliable and repeatable expansion) was developed. The device is composed of two integrated subsystems: the ratcheting mechanism, and the data acquisition and control system. To design the SMA wire and reset spring of the ratcheting mechanism, an alternative graphical design method is outlined in which the stress/strain material curves are scaled and translated into shifted austenite and martensite actuation curves (Reset View) that aid the visualization and selection of the reset spring. These transformations are based on the geometry of the ratcheting mechanism and actuation system as well as the system forces experienced by the spring including the force imposed by the ratcheting mechanism, the external force from the bowel, friction in the device, and a seal through which the mechanism extends. To predict these forces and apply the Reset View design methodology, an analytical kinematic and kinetic model of the ratcheting mechanism was developed, the safe loading range of bowel tissue was experimental measured, the force from the seal was experimental measured, and friction within the device was conservatively estimated. The design of the data acquisition and control system was guided by considerations of the implanted circuit footprint, power consumption, and wireless range. The embedded electronics programing was developed to reduce power consumption, yet enable control of the device communication parameters and a range of other device settings to make adjustments during implantations possible if needed. The integrated device has been fabricated, and both the ratcheting model and reset view design process has been validated

on the benchtop. The full device performance was validated on the benchtop and in an initial *in vivo* experiment.

Three i*n vivo* experimental studies enabled by the Instrumented SMA Driven Ratchet explored the response of the bowel different tissue expansion approaches. In the constant rate impulsive displacement control study, two sets of expansions were commanded each day of the one week distraction period. In the displacement rate limited load control study, the expansions were automatically commanded if the measured load was less than 60 gf but limited to one expansion per hour. And in constant load control trial, the expansions were automatically commanded if the measured load dropped below 45 gf with no limitation on expansions per hour. For each study, the Instrumented SMA Driven Ratchet was implanted in a Roux limb segment of small bowel isolated from the continuous gastrointestinal tract to eliminate the risk of device induced bowel obstruction. During the distraction period, the health of the animal model was observed, the applied load and displacement of the device were monitored remotely, and the device was commanded based on the tissue expansion approach. Following the distraction period, tissue samples of the distracted segment, Roux limb control, and normal bowel were taken to evaluate the health and functionality of the tissue by evaluating its morphology, transepithelial electrical resistance, and percentage of proliferating epithelial cells. Results from the tissue evaluations suggest that the distracted segments underwent true growth rather than stretching, and that the health and functionality of the tissues were preserved. The load data collected during the constant rate impulsive displacement control study suggested two interesting results: the maximum rate at which bowel is safely be grown may be much higher than previously thought and the rate at which the tissue grows and responds to expansion changes during the distraction period. As suggested by the constant rate impulsive displacement control study, when the tissue expansion approach was based on the measured load, the rate of tissue growth increased dramatically without affecting tissue health.

The development and experimental studies with the Instrumented SMA Driven Ratchet has led to medical, surgical and engineering contributions. Although intraluminal bowel pressure sensors exist in prior art, the Instrumented SMA Driven Ratchet is the first system to make *in vivo* measurements of the longitudinal load within living porcine bowel tissue. The design of the SMA driven ratcheting mechanism, an important external leveraging architecture for SMA, was developed such that it may be scaled for a wide range of applications. Furthermore, the Reset Design View Methodology, a novel design approach for directly selecting the bias element of

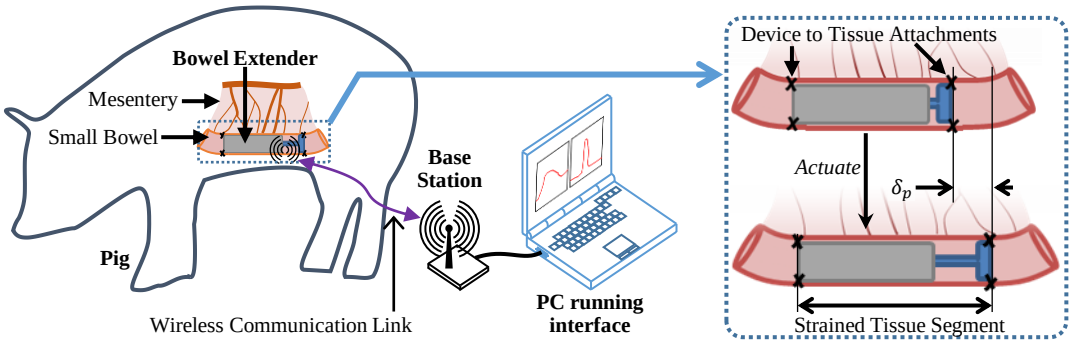


Figure 3.1. Bowel Lengthening System.
The bowel extender, which is wirelessly controlled by a user at a PC, is implanted in an isolated segment of the pig's small bowel. Bowel growth is induced by mechanotransduction as the bowel extender lengthens. Bowel tension and displacement data are wirelessly transmitted to the PC operating the user interface.

general SMA actuators reset with a bias element, was established. Results from *in vivo* experiments suggest that higher rates of bowel growth are achievable than previously thought, which is an important finding toward developing the mechanotransduction based treatment for correcting short bowel syndrome.

3.1. Device Concept

To compare the unique methods of exploiting mechanotransduction, it is important to have a versatile device that can apply relevant load or displacement profiles such as constant, ramping, and impulsive loads or displacements. To eliminate the risk of the device causing a bowel obstruction, it is implanted in a segment of small bowel tissue that is isolated from the continuity of the gastrointestinal (GI) tract as shown in Figure 3.1. The mesentery, or vasculature, of the isolated bowel segment is left intact to prevent the small bowel tissue from becoming ischemic, and the continuity of the GI tract is restored through a surgical reconnection. Within the isolated bowel segment, the Instrumented SMA Driven Ratchet is sutured to the tissue at both ends with a circular attachment. The expansion of the device can be controlled manually or automatically. In either mode, the command to actuate is transmitted wirelessly from the base station to the embedded electronics on the device which trigger the actuation of the SMA driven ratcheting mechanism. As the device expands and tensions the isolated small bowel segment, the applied load is transferred from the circular attachment to a force sensor mounted in the device. A series of electronic circuits wirelessly transmit the output of the force and displacement sensors to a PC user interface, enabling medical personnel to make informed decisions during the implantation with

regard to changing device parameters or the expansion protocol. The expansion of the device may be commanded manually or automatically to conduct displacement based studies. For load based studies, the living tissue reacts and grows in response to the device; thus, the application of load profiles is achieved by actively monitoring the load and actuating the device automatically to modify the load when necessary. For example, to maintain a constant load during the implantation period, the Instrumented SMA Driven Ratchet is actuated automatically each time the measured load decreases below the specified load as the bowel grows. This capability allows medical researchers to explore and compare different growth strategies for exploiting mechanotransduction.

The Bowel Lengthening System is composed of two major subsystems: the ratcheting mechanism, and the data acquisition and control system. The design of the two subsystems was largely decoupled due to the uncomplicated nature in which the subsystems interact. In the following section, a detailed description of each subsystem's architecture and operation is presented.

3.1.1. Ratcheting Mechanism

A key technical challenge to the bowel lengthening system is the expansion mechanism, whose function is to increase the length of the Instrumented SMA Driven Ratchet in a gradual and controlled manner, thus safely applying tension to the attached small bowel segment. Because of the desired versatility of the Instrumented SMA Driven Ratchet, passive solutions such as springs cannot be used because they do not give medical personnel the ability to conduct experiments where either the load or displacement is controlled. Thus, an actuated mechanism that can be controlled externally is required. A primary constraint on the design of the expansion mechanism is the available length and diameter of the tissue lumen, which for a pig's small bowel limits the outer diameter of the device to approximately 0.75 inches and the initial length to approximately 6.50 inches (to limit the initial stress on the mesentery). This constraint excludes bulky electrical motors along with considerations of the power required to drive them. While hydraulics can fit into this constrained space, safe and reliable displacement control is difficult to achieve due to friction between the piston and cylinder, and the compliance of the hydraulic line. The need for a compact and energy dense actuator that can fit within the slender form factor of the Instrumented SMA Driven Ratchet is met exceptionally well by SMA wire, which can produce strains of 2 to

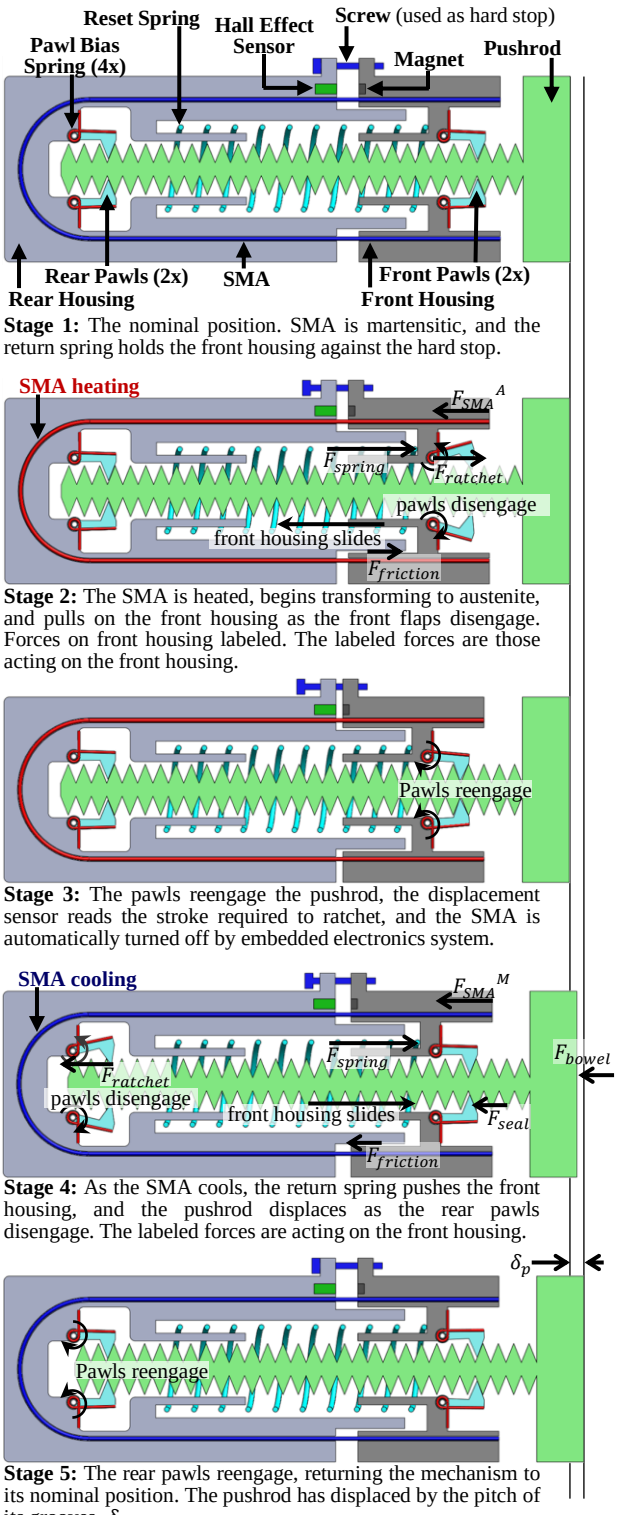
8% against moderate loads, with lower strains advised for high cycle applications. To reduce the length of the actuator/device, the SMA strain can be leveraged through the use of a ratcheting mechanism, which accumulates the small displacements generated by the SMA wire during operation. The ratcheting mechanism maintains the expansion of the Instrumented SMA Driven Ratchet against external loads without requiring any power, which is advantageous because the power drawn by the device is supplied by a battery rather than a power supply. Another feature of the ratcheting mechanism is that the expansion of the device at each SMA actuation is inherently predictable and repeatable, as it is defined by the pitch of the grooved pushrod.

3.1.1.1. Ratcheting Mechanism Architecture

The ratcheting mechanism, whose architecture and operation is shown in Figure 3.2, accumulates small displacements given by the SMA wire into a much greater net expansion of the device. The ratcheting mechanism consists of two front pawls, hinged within the front housing which slides axially relative to the rear housing, two rear pawls, hinged within the rear housing, a grooved pushrod (rack), which slides through the housings and engages with the pawls, and an SMA wire actuator and its reset spring, which induces relative motion between the housings and therefore the pawl sets. The SMA wire actuator is attached to and routed through the front housing, around a semicircular bend in the rear housing, and back through and attached to the front housing. This routing path is mirror symmetric about the axis of the device, enabling the SMA actuator to pull on the front housing without creating a moment that could cause the front and rear housing to bind. In this routing configuration, the SMA wire actuator essentially acts like two parallel wires fixed to the front and rear housing; thus, in the model-based design of the ratcheting mechanism described in this paper, the single SMA wire actuator will be treated as two separate parallel wires. A screw passed through a clearance hole on the rear housing and threaded into the front housing provides an adjustable hard stop, which limits the martensitic strain of the SMA actuator and sets the displacement of the front housing relative to the rear housing when the SMA is cool. A Hall Effect sensor, which measures magnetic field strength, is fixed to the rear housing, and a permanent magnet is fixed to the front housing. Because of this, the output of the Hall Effect sensor varies with the displacement of the front housing relative to the rear housing and can be used to measure the strain of the SMA wire during operation.

3.1.1.2. Ratcheting Mechanism Operation

The cyclic linear ratcheting motion is shown in five labeled stages in Figure 3.2. In Stage 1, which is the nominal stage of the device, the front housing (a) is held in place by an adjustable hard stop (b) against the force produced by the reset spring (c), which strains the SMA wire by the distance set with the adjustable hard stop. The SMA wire is mounted between the rear housing (e) and the front housing such that as the SMA contracts, the front housing moves toward the rear housing. In the nominal position, the rear ratchet pawls (f) hold the pushrod (g) rigidly in place against external loads. Stage 2 begins when the command to actuate is received by the electronics that drive the SMA wire. In this stage, the SMA wire is actuated via joule heating, which causes the material to transform from martensite to austenite. During the transformation the actuator contracts, which causes the front ratchet pawls to disengage, opening outward against the force from a set of pawl bias springs (h), and causes the reset spring to compress as the front housing moves toward the rear housing. The relative motion between the front and rear housing is measured by a permanent magnet (i) and a Hall Effect sensor (j) whose output is linear with respect to the measured magnetic field strength. During Stage 3, the motion of the front housing relative to the rear housing continues until the measured displacement exceeds a user defined limit set to ensure the stroke of the actuator is enough for the pawl bias springs to force the pawls to reengage in the adjacent groove of the pushrod. When this event occurs, the power to the SMA is automatically stopped by the driving circuitry and the SMA is allowed to cool. In Stage 4, the SMA cools and transforms back to martensite from austenite. During this transformation, the reset spring pushes the front housing away from the rear housing, causing the pushrod to move forward due to its engagement with the front pawls, which in turn causes the rear pawls to disengage and the force of the bowel tissue to increase as it is strained. As the pushrod moves forward, its motion is opposed by friction within an annular seal (not shown) through which the pushrod moves. The relative motion continues in Stage 5 until the rear pawls have been reengaged by the pawl bias springs into the next groove on the pushrod, and the front housing is once again held in place against the adjustable hard stop, thus displacing the pushrod by the pitch of its grooves and resetting the mechanism to its nominal stage. During operation, the applied tensile force on the small bowel tissue is measured by a compression load cell mounted on the end of the device opposite the pushrod. The displacement of the device is found by multiplying the number of successful steps, as verified by the output of the Hall Effect sensor, by the pitch of the grooved



Stage 1: The nominal position. SMA is martensitic, and the return spring holds the front housing against the hard stop.

Stage 2: The SMA is heated, begins transforming to austenite, and pulls on the front housing as the front flaps disengage. Forces on front housing labeled. The labeled forces are those acting on the front housing.

Stage 3: The pawls reengage the pushrod, the displacement sensor reads the stroke required to ratchet, and the SMA is automatically turned off by embedded electronics system.

Stage 4: As the SMA cools, the return spring pushes the front housing, and the pushrod displaces as the rear pawls disengage. The labeled forces are acting on the front housing.

Stage 5: The rear pawls reengage, returning the mechanism to its nominal position. The pushrod has displaced by the pitch of its grooves, δ_p.

Figure 3.2. Operation of Ratcheting Mechanism.

The operation of the ratcheting mechanism is shown in five stages, which are repeated to accumulate a displacement, δ_p, at each step against the external load from the small bowel, F_{bowel}.

pushrod. To follow an experimental lengthening profile based on the applied displacement or load, multiple actuations may be automatically or manually commanded from the user interface. For example, to automatically maintain an applied load, the device may be lengthened each time the measured load decreases below a specified tension threshold. As the Instrumented SMA Driven Ratchet is lengthened, the isolated small bowel segment enclosing the device is tensioned and thus grown via mechanotransduction.

3.1.2. Data Acquisition and Control System

The data acquisition and control system enables the measurement of the applied bowel tension and displacement, drives the SMA wire in the ratcheting mechanism, and creates a wireless link between the medical personal and the implanted Instrumented SMA Driven Ratchet that enables continuous monitoring and control of the experiment.

3.1.2.1. Data Acquisition and Control System Architecture

The data acquisition and control system is a set of three circuits: the Bowel Extender Circuit, the Pack Circuit, and the Base Station Circuit, as shown in Figure 3.3. The Bowel Extender Circuit is composed of a microcontroller that samples the output of the Hall Effect sensor and the amplified output of the load sensor, drives the SMA actuator with a MOSFET, and communicates with the wireless Pack Circuit with a wired serial connection. The amplification of the load sensor output is achieved by an instrumentation amplifier whose gain is controlled by a digital potentiometer interfaced with the microcontroller. The Pack Circuit is made up of a microcontroller that interfaces with a wireless transceiver for communication with the Base Station, and is embedded in a housing containing the battery powering both implanted circuits. The base station, which is not implanted, acts as a two-way communication relay between the PC interface and the implanted electronics, and is composed of a microcontroller that interfaces with a wireless transceiver for communication with the implanted electronics, and a line driver/receiver for communication with the PC.

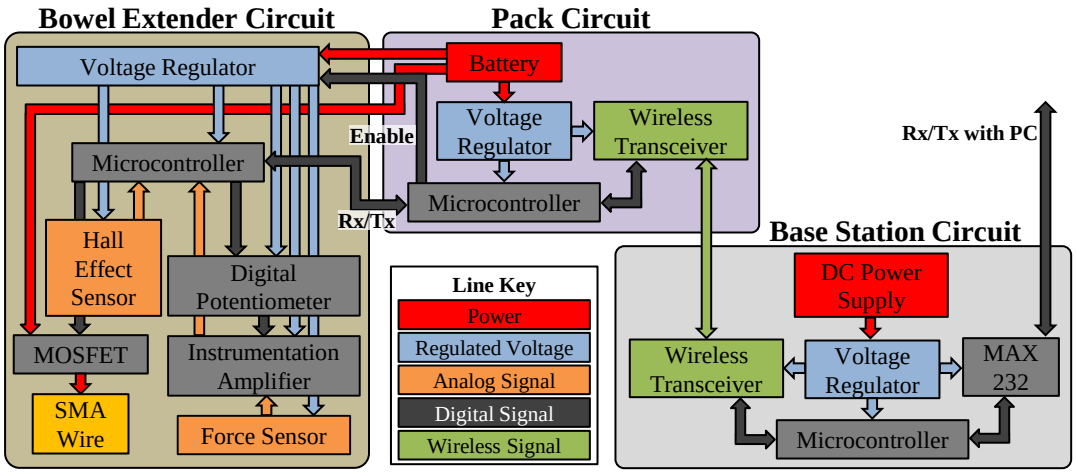


Figure 3.3. Data Acquisition and Control System Architecture.

The data acquisition and control system architecture is composed of three separate but interfaced circuits: the Bowel Extender Circuit, which drives the SMA wire actuator and conditions the outputs of the load and displacement sensors, the Pack Circuit, which houses the battery and wirelessly communicates with the Base Station Circuit, and the Base Station Circuit, which relays data and commands between the Pack Circuit and a PC running the user interface.

3.1.2.2. Data Acquisition and Control System Operation

The operation of the electronics was developed to establish the flow of sensor data and user input commands between the three circuits and the PC interface while simultaneously conserving battery power. Nominally, the Instrumented SMA Driven Ratchet is not actuating and the operation of the electronics follows the sequence diagram shown in Figure 3.4. To conserve the battery, the Bowel Extender Circuit is turned off by a digital signal from the Pack Circuit that enables and disables the voltage regulator of the Bowel Extender Circuit. At the start of the operation sequence, the Pack Circuit turns the Bowel Extender Circuit on and sends the following user defined parameters: the command to run the SMA actuation sequence (true or false), the displacement sensor threshold used during an actuation (integer), and the gain of the instrumentation amplifier (integer). The Bowel Extender Circuit then samples the displacement sensor and the amplified load sensor and sends the data to the Pack Circuit. Upon receiving the sensor data, the Pack Circuit immediately turns the Bowel Extender Circuit off. The sensor data are then concatenated with the measured battery voltage and if a parameter of the Pack Circuit has been altered, the new value of that parameter for verification. The augmented set of data is then sent from the Pack Circuit to the Base Station Circuit wirelessly, where it is relayed to the PC user

interface. The data are displayed immediately to enable informed decision making by the medical personal. From the user interface, the medical personal may queue commands to the Pack Circuit via the Base Station Circuit to actuate the Instrumented SMA Driven Ratchet (true or false) or to change a parameter including the displacement sensor threshold, the instrumentation amplifier gain, the SMA power timeout, and the rate of data acquisition. Upon receiving new parameters from the Base Station Circuit, the Pack Circuit "sleeps" to conserve battery power for an amount

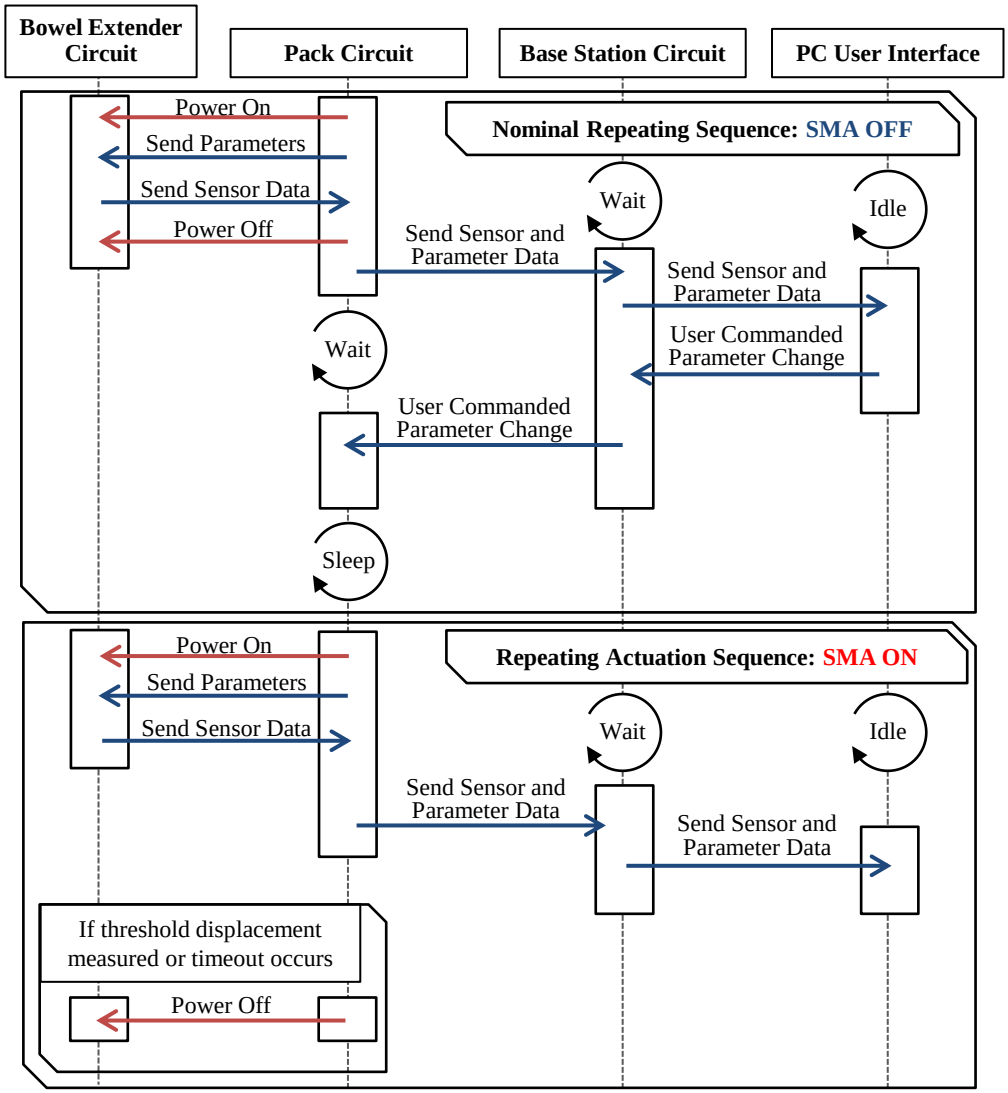


Figure 3.4. Data Acquisition and Control System Operation.

The operation of the data acquisition and control system consists of two separate modes, the Nominal Repeating Sequence, in which data/commands are sent/received by the Bowel Extender Circuit and the SMA actuator is not powered, and the Repeating Actuation Sequence, in which commands are not sent to the Bowel Extender Circuit to increase the data rate and the SMA actuator is powered. The operation was developed to maximize the time in which the implanted electronics are off or in a low power consumption mode to conserve battery capacity and enable experiments up to two weeks in length.

of time specified by the desired rate of data acquisition. Any user commanded change to the set of parameters is applied in the operation sequence shown in Figure 3.4. The operation of the electronics is different while the SMA wire is being actuated to drive the ratcheting mechanism in that the flow of data is one-way rather than two-way (to increase the data acquisition rate), and the power of the Bowel Extender Circuit is not cycled by the Pack Circuit between data points. The power to the SMA wire and Bowel Extender Circuit is supplied until one of two conditions is met: 1) the measured output of the displacement sensor exceeds the user defined threshold, or 2) the user defined SMA timeout occurs. The SMA timeout prevents unsafe overheating of the SMA wire in the event that the Hall Effect sensor fails or the Ratcheting Mechanism is blocked. When either condition is met, the actuation sequence is exited and electronic subsystem returns to the nominal operating sequence. Although not shown (for clarity) in Figure 3.4, the Pack Circuit and Base Station Circuit are programmed with timeouts to prevent them from hanging when the Base Station Circuit transceiver is out of wireless range with the Pack Circuit. These timeouts also ensure that the Pack Circuit does not needlessly consume battery power when it is out of range from the Base Station Circuit.

3.2. Ratcheting Mechanism Design

The analytical design of the SMA driven ratcheting mechanism was completed by developing the Reset View Design Methodology, an alternative to the traditional graphical design method for SMA actuators; by developing a model to guide the design of a parameterized ratchet pawl and rack geometry; and by deriving a model of the force interaction between the pawls and rack. Although used in this dissertation to design an SMA driven ratcheting mechanism, the Reset View Design Methodology is a general approach for designing SMA actuators that are re-strained by a bias element or reset spring. Additionally, the ratchet models presented herein are scalable and may be applied to the design of ratcheting mechanisms for automotive, aerospace, and other medical applications.

3.2.1. Reset View Design Methodology

Constitutive models describing the behavior of SMA wire continue to be an active research topic, and as such, most SMA driven mechanisms are designed with a graphical approach using austenite and martensite stress/strain relations acquired experimentally. Although the common graphical approach is used to specify the SMA wire parameters (diameter and length) given

knowledge of the system loads that act on the actuator and its desired stroke, practically, designers have many fewer SMA wire design options to choose from than they have system parameters such as the stiffness of the reset spring. This is especially true for the Instrumented SMA Driven Ratchet, where the size of the device strongly constrains the length of the SMA wire and the general constraint of the limited number of commercially available SMA wire diameters.

To overcome the limited design space of the SMA actuator within the Instrumented SMA Driven Ratchet, the traditional graphical method was adapted such that the SMA wire parameters are specified first, and then the parameters of a reset spring are determined to allow the actuator to produce the desired stroke. To formulate this new graphical process, the experimentally acquired SMA stress/strain material curves are transformed into force/displacement SMA curves by scaling the stress and strain curves by the cross-sectional area of the SMA wire and the SMA wire length, respectively. To acquire the Reset View, the force/displacement SMA curves are further transformed by the shifting them by the system loads. After completing these transformations, the resulting view enables the designer to quickly determine the maximum stiffness of a reset spring that will produce the desired stroke. This process may be repeated to identify appropriate springs for each SMA wire diameter considered for the ratcheting mechanism.

This section formulates the Reset View graphical method with details on the transformations and spring selection process. For the Instrumented SMA Driven Ratchet, the system loads that must be determined include the axial components of the external load provided by the tension of the isolated small bowel segment, F_{bowel}, the load due to the ratcheting mechanism, $F_{ratchet}$, the friction force from the annular seal on the pushrod, F_{seal}, and the force of friction in the sliding components of the device, $F_{friction}$. To predict the loads associated with the ratcheting mechanism, a general ratcheting model is derived in Section 3.2.2. The range of safe loads that can be applied to pig small bowel tissue is evaluated experimentally, as described in Section 3.3.1. The seal force, F_{seal}, was identified experimentally, as described in Section 3.3.2. The axial component of the force of friction, $F_{friction}$, is highly dependent on the physical prototypes and is not typically known prior to design, so it was conservatively estimated. The entire process is performed for the design of the Instrumented SMA Driven Ratchet in Section 3.3.

3.2.1.1. Transformation from Material Stress-Strain to Engineering Force-Displacement

The Reset View design process begins with the experimentally measured austenite and martensite stress/strain material curves. To transform the material curves into load/displacement curves, the SMA wire parameters of length and diameter must be defined. A lower bound on the diameter of the SMA wire is determined by finding a lower bound on the maximum force subjected to the SMA wire in its austenite state and selecting the smallest wire diameter that keeps the corresponding stress below the manufacturer's recommended maximum stress. For an SMA driven ratcheting mechanism, like the device described herein, that expands while the SMA is re-strained by the reset spring, the loads acting on the actuator differ in the martensite and austenite phases.

As the SMA is heated, as shown in operation stages 2 and 3 of Figure 3.2, the external axial load is not transmitted through the SMA. Rather, that load is transmitted through the rear ratchet pawls, which rigidly hold the pushrod in place. Thus, the pair of austenitic SMA wires are subjected only to a load, ${F_{SMA}}^{A}$, given by the sum of the reset spring force, F_{spring}, the axial component of the sliding friction force within the device, $F_{friction}$, and the axial component of the forces generated by the interaction of the pushrod with the front ratchet pawls, $F_{ratchet}$, such that

$$ {F_{SMA}}^{A} = F_{spring} + \underbrace{F_{friction} + F_{ratchet}}_{{F_{sys}}^{A}}, \tag{1} $$

where ${F_{sys}}^{A}$ represents the sum of the system loads experienced by the austenitic SMA wires excluding the spring load.

As the SMA is allowed to cool, as shown in operation stages 4 and 5 of Figure 3.2, the external axial load from the bowel, F_{bowel}, is transmitted to the SMA through the front ratchet pawls. In these operational stages, the load subjected to the pair of martensitic SMA wires, ${F_{SMA}}^{M}$, is the spring load minus the sum of the axial components of the force of friction, the force generated by the interaction of the pushrod with the rear ratchet pawls, the force produced by the seal, and the external load from the bowel such that

$$ {F_{SMA}}^{M} = F_{spring} - \underbrace{\left(F_{ratchet} + F_{friction} + F_{seal} + F_{bowel}\right)}_{{F_{sys}}^{M}}, \tag{2} $$

where ${F_{sys}}^{M}$ represents the sum of the system loads subjected to the martensitic SMA wires, excluding the spring force.

To bound the SMA wire diameter required to transform stress into force, the maximum value of the austenitic SMA load is predicted using Equation 1, but the force from the spring is not known. A minimum SMA wire diameter is determined by assuming that the spring provides just enough force to reset the mechanism without needing to reset the martensitic SMA. This allows the generation of a bound without knowing the bounding SMA wire diameter *a priori*. The spring force that meets this requirement is found by setting the force from the pair of martensitic SMA wires, ${F_{SMA}}^{M}$, to zero in Equation 2 and solving for the spring force, F_{spring}. The resulting minimum spring force substituted into Equation 1 provides a lower bound of the maximum value of the force, ${F_{sma}}^{A}$, provided by the pair of austenitic SMA wires as

$$\begin{aligned} {F_{sma}}^{A}\big|_{max} &= {F_{sys}}^{A} + {F_{sys}}^{M} \\ &= F_{bowel} + F_{seal} + 2\left(F_{friction} + F_{ratchet}\right). \end{aligned} \tag{3}$$

The maximum available force from the pair of austenitic SMA wires depends on their total cross-sectional area and the maximum allowed stress, σ_{max}, in the austenite state, generally specified by the SMA wire manufacture to provide a long lifetime of the wire and to minimize performance degradation due to shakedown [9],

$${F_{sma}}^{A}\big|_{max} = 2\sigma_{max}\frac{\pi}{4}{d_{min}}^{2}, \tag{4}$$

where d_{min} is the minimum allowable diameter which maintains the stress below the specified maximum. This minimum diameter can be solved by equating Equations 3 and 4 as

$$d_{min} = \sqrt{\frac{2}{\pi}\left(\frac{F_{bowel} + F_{seal} + 2\left(F_{friction} + F_{ratchet}\right)}{\sigma_{max}}\right)}. \tag{5}$$

The minimum value of the SMA diameter is rounded up to next commercially available SMA wire diameter to select the first candidate wire diameter. One or more larger wire diameters may be selected as candidates in addition since d_{min} provides a lower bound only and may not be sufficient to actuate against available reset springs.

In the design of compact SMA driven mechanisms, the maximum possible length of the SMA wire is often used to reduce the strain of the actuator, given a desired stroke, to maintain a long

lifetime of the wire [9]. Thus, the length of the SMA wire may be determined by the physical constraints of the device. If physical constraints are not an issue, the length of the SMA wire may be determined conservatively by dividing the desired stroke, δ, by the operating strain of the SMA wire.

With the values of the SMA wire parameters identified, the stress/strain material curves are transformed to engineering force/displacement by multiplying the stress by the total cross sectional area of the two wires to obtain force, and multiplying the strain by the length of each wire to obtain displacement. This engineering view is commonly used in actuator design as it provides a useful visualization in cases with a simple system load, and where the specific contributions of various system loads and the SMA wire parameters are subject to design changes [10]. In the Instrumented SMA Driven Ratchet, however, the SMA wire dimensions are fixed due to the particularly tight packaging constraints within the device, leaving the reset spring as the primary component subject to design. Also, the system loading in the Instrumented SMA Driven Ratchet is different in the heating and cooling portions of the actuation cycle. In the engineering view, the coupled relationship between the two parts of the cycle is unclear, and a new view is required which allows for visualization of these varying loads with respect to the reset spring.

3.2.1.2. Transformation from Engineering Force-Displacement to Reset View

In the design of the Instrumented SMA Driven Ratchet, the various system loads can be predicted prior to design. This allows these loads to be decoupled and grouped with the two material curves, shifting them into a different coordinate frame, thus creating a unique view which isolates the reset spring. To isolate the load on the spring, the system forces in Equations 1 and 2 may be recast as

$$\begin{aligned} {F_{spring}}^{A} &= {F_{SMA}}^{A} - {F_{sys}}^{A} \\ &= {F_{SMA}}^{A} - (F_{friction} + F_{ratchet}) \end{aligned} \tag{6}$$

$$\begin{aligned} {F_{spring}}^{M} &= {F_{SMA}}^{M} + {F_{sys}}^{AM} \\ &= {F_{SMA}}^{M} + \left(F_{ratchet} + F_{friction} + F_{bowel}\right) \end{aligned} \tag{7}$$

The right hand side of Equations 5 and 6 are graphically depicted as a downward shift of the austenite curve by ${F_{sys}}^{A}$ and an upward shift of the martensite curve by ${F_{sys}}^{M}$, as shown in Figure 3.5c. This final transformation leads to the Reset View, where the shifted austenite and martensite

curves, $\hat{F}_{sma}{}^{A} = F_{SMA}{}^{A} - F_{sys}{}^{A}$ and $\hat{F}_{sma}{}^{M} = F_{SMA}{}^{M} + F_{sys}{}^{M}$, are plotted. Since this transformation is into the force-deflection space of the reset spring, the parameters of an appropriate reset spring can be directly found from the Reset View.

3.2.1.3. Reset Spring Selection

To determine the maximum reset spring stiffness that will produce the desired stroke, the hard stop location, d_{hs}, and desired stroke, δ, must be determined by the designer. An important element of the device's ratcheting mechanism is its adjustable hard stop, which is used to limit the martensite strain of the device, limit the expansion of the device to one groove of the pushrod, and mitigate the effect of SMA performance degradation [9]. For the ratcheting mechanism, a small incremental expansion of the device can be specified to enable fine adjustments to the load or displacement applied to the bowel. This desired stroke, δ, is usually selected conservatively as some amount greater than the groove pitch, δ_p, of the pushrod, and determines the appropriate position of the hard stop. The hard stop is separated by the stroke length from the point **A** on the transformed austenite SMA curve, which intersects the horizontal line defined by the maximum allowable SMA force $F_{sma}{}^{A}\big|_{max}$ transformed into the reset view (*i.e.* shifted downward by $F_{sys}{}^{A}$). Therefore, the maximum spring stiffness equals the slope of the line connecting two points: 1) the point **A,** where the transformed maximum force line intersects the transformed austenite curve (at position $d_{hs} - \delta$) , and 2) the point **B,** where the vertical line at the hard stop position intersects the transformed martensite curve (at position d_{hs}) as shown in Figure 3.5d,

$$k_{max} = \frac{\hat{F}_{sma}{}^{A}\big|_{d_{hs}-\delta} - \hat{F}_{sma}{}^{M}\big|_{d_{hs}}}{\delta}. \tag{8}$$

This is the maximum feasible spring stiffness that gives the desired stroke, since a larger stiffness line will intersect the transformed austenite and martensite curves at points horizontally closer together than the desired stroke. By using a more compliant reset spring, the design becomes robust to unexpected increases of the external load, ratcheting load, or friction load by intersecting the vertical hard stop line at a larger value of force. If a reset spring with a stiffness below the maximum value cannot be found, the SMA wire diameter should be increased to the next largest available diameter, the SMA curves re-transformed, and Equation 8 reapplied. The Reset View allows the direct visualization of the impacts of changes in reset spring selection and is useful to

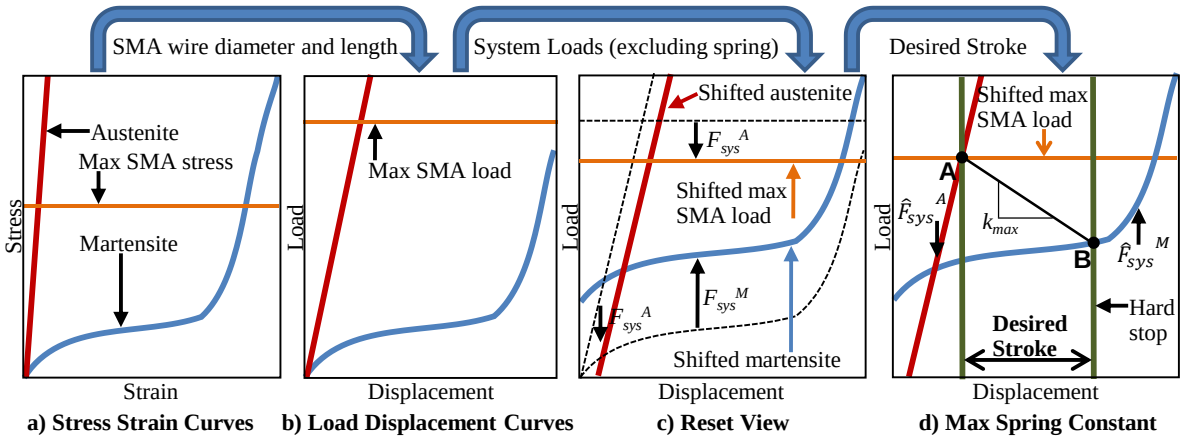


Figure 3.5. Reset View Design Process.
The austenite and martensite curves (a) are scaled from stress/strain to load/displacement (b) based on the SMA diameter and length, adding in a max SMA load line from the maximum recommended SMA stress. The Reset View (c) is created from this engineering view by shifting the martensite curve up by $F_{sys}{}^{M}$, and shifting the max SMA load and austenite curves down by $F_{sys}{}^{A}$. In this view, an appropriate reset spring is easily specified (d).

guide the selection when considering issues such as robustness to unexpected external loads and additional safety factors in stroke.

To apply the Reset View design methodology, the values of $F_{sys}{}^{M}$ and $F_{sys}{}^{A}$ must be determined. For the Instrumented SMA Driven Ratchet, the forces that contribute to $F_{sys}{}^{M}$ and $F_{sys}{}^{A}$ are the ratcheting force, predicted by an analytic model developed in the next section, the maximum expected external force from the tension of the small bowel tissue, experimentally characterized in Section 3.3.1, the seal force on the pushrod, which was measured with a rod similar in size to the pushrod and the seal material, and the force of friction, which is conservatively estimated.

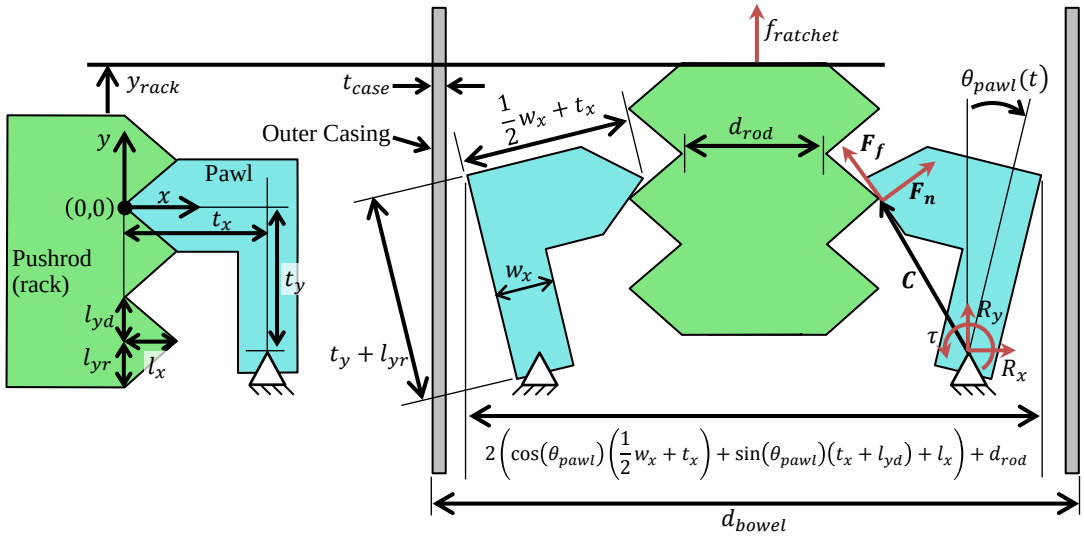
3.2.2. Analytical Ratchet Model

The Reset View requires a prediction of the force, $F_{ratchet}$, within the ratchet mechanism to define the transformations of the SMA material curves. Predicting this force requires the selection of the rack tooth and pawl geometry which is selected based on packaging constraints, load bearing capacity, self-locking condition, and a slide/skip mode reengagement requirement. For a given tooth and pawl geometry, an analytical kinematic model of the ratchet is developed which provides the relationship between the rack displacement and pawl angle as the pawls are disengaged. This kinematic model is used in an analytical quasi-static kinetics model to predict the force required

to displace the rack while disengaging the pawls against their bias springs. This force is used as one component of the shifting transformation in the Reset View methodology.

3.2.2.1. Tooth and Pawl Geometry

Five length parameters define the pawl and profile of the pushrod referenced in the fully engaged position shown in Figure 3.6a: the x (normal to the pushrod) and y (along the pushrod) components of the distance from the pivot to the tip of the pawl, t_x and t_y, the depth of the pawl and pushrod teeth, l_x, and the pitch of the teeth $\delta_p = l_{yd} + l_{yr}$, where asymmetric profiles are allowed ($l_{yd} \neq l_{yr}$). These parameters define the geometry of the mechanism while the pawls are engaged, supporting a load, and while the pushrod is displaced by the actuation system a distance, y_{rack}, measured relative to the fully engaged position, causing the pawls to disengage, rotating by an angle θ_{pawl} (Figure 3.6b). The design of the geometric parameters that define the pawl and rack must balance requirements governed by several factors: physical space constraints of the small bowel lumen, the load bearing capacity of the rack and pawl teeth, the self-locking condition, and the desired slide/skip reengagement behavior of the ratcheting mechanism.



a). Fully Engaged **b). Pawls Disengaging** (Rotating away from pushrod)

Figure 3.6. Geometry of Ratchet Model.

Five geometric parameters are introduced to develop the kinematics of the rack and pawl: t_x, t_y, l_{yd}, l_{yr}, and l_x. The length and width of the pawl are defined by t_y and t_x, respectively, and l_{yd}, l_x, and l_{yr} define the profile of the rack. The kinematics define the angle of the pawl, θ_{pawl}, as function of the rack displacement, y_{rack}.

3.2.2.1.1. Packaging Constraint

These five geometric parameters must be selected such that throughout the rack displacement, y_{rack}, the entire mechanism fits within the lumen of the bowel defined by its inner diameter, d_{bowel}, which restricts the dimensions of the pushrod and pawls as illustrated in Figure 3.6b. For the mechanism and its casing to fit within the bowel, the largest width of the ratchet components when the pawls are disengaged to their maximum angle, $\theta_{tip} = \max \theta_{pawl}$, must be less than the inner diameter of the bowel minus twice the thickness of the outer casing, such that

$$2\left(\cos(\theta_{tip})\left(\frac{1}{2}w_x + t_x\right) + \sin(\theta_{tip})(t_x + l_{yd}) + l_x\right) + d_{rod} < d_{bowel} - 2\,t_{case}. \tag{9}$$

3.2.2.1.2. Load Bearing Capacity

In addition to meeting this packaging constraint, the dimensions of the pushrod grooves and pawl teeth must be designed to bear the external load on the mechanism without yielding. This requirement may be met analytically using approximation equations such as those appearing in textbooks for the design of gear teeth and power screws [11], or numerically using standard FEM analysis. The pushrod diameter is designed to satisfy the Euler buckling criterion, and its length is guided by the desired net expansion of the device.

3.2.2.1.3. Self-Locking Condition

When bearing a load, the pawls must remain engaged and not be forced outward, allowing the ratchet to be back-driven. The geometry of the pawls and teeth determine whether the mechanism is self-locking without help from friction or the bias springs. The self-locking condition is derived geometrically by ensuring that the line of action of the force from the rack on the pawl, perpendicular to the pawl contact face and defined by the angle β_1, induces an inward moment about the pawl hinge, as shown in Figure 3.7. This angle must be less than the angle β_2 which defines the line connecting the center of this contact face to the hinge center. In terms of the tooth and pawl geometric parameters, this criterion can be expressed as

$$\frac{l_{yr}}{l_x} < \frac{t_x - \frac{1}{2}l_x}{t_y + \frac{1}{2}l_{yr}}. \tag{10}$$

3.2.2.1.4. Pawl Reengagement Slide / Skip Mode

There are three possible configurations for the interaction between the pawl and rack as the pushrod is actuated forward depending on the tooth and pawl geometry: slide, skip, and slide/skip. In the skip configuration, the pawl does not contact this surface at all, but immediately skips to the front face of the next tooth on the rack under the action of the pawl bias springs. In the slide/skip configuration, the tip of the pawl contacts the back surface of the rack tooth during only the first part of the reengagement, and skips to the next tooth after sliding a portion of the distance down the tooth. In the slide configuration, the tip of the pawl contacts the back surface of the rack tooth for the entire reengagement. Sliding during reengagement needs to be avoided since sliding friction can cause extra wear, and can cause the pawls to bind and not properly reengage. To avoid the full slide configuration, the tooth and pawl geometry must be designed such that the arc traced by the pawl tooth tip around its hinge is at least tangent to the back face of the tooth when the pawl is fully engaged,

$$\frac{l_{yr}}{l_x} < \frac{t_x}{t_y}. \tag{11}$$

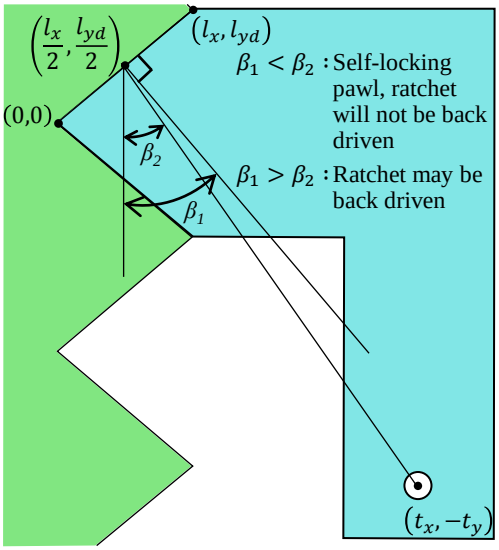


Figure 3.7. The Self Locking Criterion.
If the net moment on the pawl tends to rotate the pawl toward the pushrod, the mechanism is self-locking (without the aid of friction) and cannot be back-driven unless the teeth on the pawl or pushrod are sheared.

A more restrictive condition is that the tooth and pawl geometry completely avoid sliding, where the skip configuration requires that the tangency condition be satisfied at the tooth tip such that

$$\frac{l_{yr}}{l_x} < \frac{t_x}{t_y} + \frac{2t_y}{2t_x - l_x} - 2\sqrt{\frac{{t_y}^2 + (2t_x - l_x)l_x}{l_x - 2t_x}}. \tag{12}$$

The self-locking criterion (Equation 10) is closely related to these two conditions, as both are derived based on the direction of the tooth/pawl contact normal and the pawl hinge tangent line relative to the hinge point. Requiring the skip configuration (Equation 12) implies that the self-locking criterion is met, while the self-locking criterion implies that the full slide configuration is avoided (Equation 11). Therefore, the skip configuration, the most restrictive condition of these three, provides the design criterion which, in combination with the packaging constraint (Equation 9) and the requirement that the teeth bear the axial pushrod loads without yielding provides the basis for selecting the geometry of the rack teeth and pawls.

3.2.2.2. Ratchet Force Model

Given the tooth and rack geometry, the force required by the actuation system to disengage the ratchet, $F_{ratchet}$, is computed. To calculate this force, the kinematics are defined which relate the angle of the pawl, θ_{pawl}, as the rack is displaced y_{rack} by the actuator, disengaging the pawls. From this relationship, the corresponding force required by the actuator is derived from the ratchet disengagement kinetics as a function of the pawl angle and rack displacement from which the peak value may be computed.

3.2.2.2.1. Ratchet Disengagement Kinematics

The ratchet disengagement kinematics model provides the pawl angle, θ_{pawl}, as a function of the rack displacement, y_{rack}, while the pawl disengages (rotates away from the rack). The kinematics are derived by defining the vector $\boldsymbol{C}$ as the relative position of the contact point between the pawl face and the tip of the rack tooth relative to the pawl pivot as shown in Figure 3.8. Since the displacement of the rack under the influence of the actuation system is only vertical, the x component of this vector remains constant while the y component changes with the vertical displacement of the rack, y_{rack}, such that

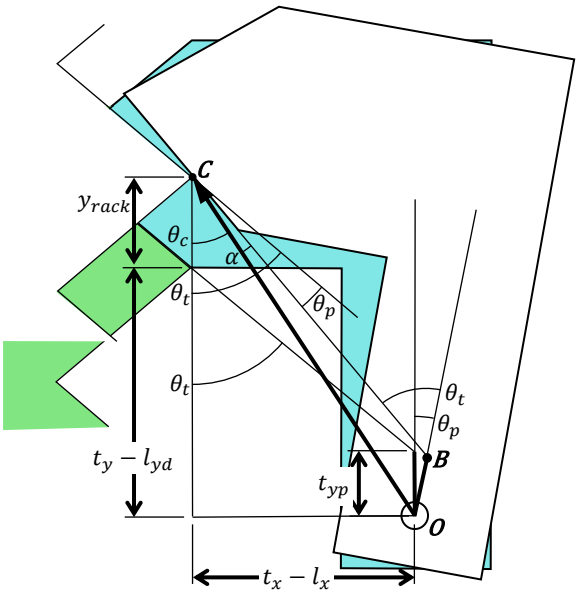


Figure 3.8. Geometric Definitions of Disengagement Kinematics.
The geometric definitions concerning the disengagement kinematics of the pawls are shown. The contact vector, $\boldsymbol{C}$, relates the rack displacement, y_{rack}, to the angle of the pawl, θ_p.

$$\boldsymbol{C} = \begin{bmatrix} l_x - t_x \\ y_{rack} + t_y - l_{yd} \end{bmatrix}. \tag{13}$$

Relating this vector to the angle of the pawl requires the definition of two fixed geometric parameters which are properties of the rack and pawl geometry, the tooth angle, θ_t, and the pawl base length, t_{yp}. The tooth angle, θ_t, is the angle relative to the y axis of the contact face between the pawl and the rack when the pawl is fully engaged and is expressed in terms of the rack geometric parameters as

$$\theta_t = \operatorname{atan}\frac{l_x}{l_{yd}}. \tag{14}$$

The pawl base length, t_{yp}, is the length of the line along the y axis connecting the pawl pivot point to the intersection of the extension of the pawl contact face and the y axis. Referencing the fully engaged position, the pawl base length is

$$t_{yp} = t_y - l_{yd} - \frac{t_x - l_x}{\tan\theta_t}. \tag{15}$$

The pawl angle, θ_{pawl}, is the difference between the tooth angle, θ_t, and the sum of two additional angles, θ_c and α, which vary with y_{rack} as shown in Figure 3.7. The first of these angles, θ_c, is defined between the vector $\boldsymbol{C}$ and the y axis.

$$\theta_c = \text{atan}\frac{t_x - l_x}{y_{rack} + t_y - l_{yd}}. \tag{16}$$

The second of these angles, α, is defined between the vector $\boldsymbol{C}$ and the contact face of the pawl. This angle is computed using the law of sines for the triangle defined by the pawl pivot, **O**, the contact point at the head of $\boldsymbol{C}$, and the intersection point **B** between the extension of the pawl contact face and the centerline of the pawl rotated an angle θ_{pawl} from the y axis (which lies at a distance t_{yp} from the pivot). The law of sines for this triangle states that

$$\frac{t_{yp}}{\sin\alpha} = \frac{\|\boldsymbol{C}\|}{\sin(\pi - \theta_t)}. \tag{17}$$

Substituting the definition of $\boldsymbol{C}$ (Equation 13) and solving for the angle α yields

$$\alpha = \text{asin}\frac{t_{yp}\sin\theta_t}{\sqrt{(t_x - l_x)^2 + \left(y_{rack} + t_y - l_{yd}\right)^2}}. \tag{18}$$

Using these definitions of the angles θ_c and α, the pawl angle, θ_{pawl}, can be expressed in terms of the rack displacement as

$$\theta_{pawl} = \theta_t - (\theta_c + \alpha), \tag{19}$$

where θ_t is constant and θ_c and α are functions of the rack displacement, y_{rack}, according to Equations 16 and 18. This equation for θ_{pawl} provides the kinematic relationship which is used to compute the forces within the ratchet mechanism that are later used in the design process of the actuation system.

This kinematic expression for the pawl angle in terms of the rack displacement is valid as the rack displaces until the tip of the pawl contacts the tip of the rack tooth at a critical displacement, y_{tip}. In the skip mode of the ratchet, this displacement is larger than the tooth pitch since after the tip configuration is reached the pawl skips down to contact the next rack tooth, passing the next fully engaged position. To find this displacement, the length of the vector $\boldsymbol{C}$ is set equal to the distance from the pawl pivot to the pawl tooth such that

$$\|\boldsymbol{C}\|_{y_{rack}=y_{tip}} = \sqrt{{t_x}^2 + {t_y}^2}. \tag{20}$$

Substituting the definition of $\boldsymbol{C}$ (Equation 13) and solving for y_{tip} yields

$$y_{tip} = l_{yd} - t_y + \sqrt{{t_y}^2 + 2l_x t_x - {l_x}^2}. \tag{21}$$

This displacement provides the maximum pawl angle, θ_{tip}, by substituting into the kinematics expression for θ_{pawl} (Equation 19), thus determining the maximum pawl angle used in the packaging constraint in Equation 9 when designing the geometry of the teeth and pawls.

3.2.2.2.2. Ratchet Disengagement Kinetics

The force, $F_{ratchet}$, applied by the actuation system as the pushrod is advanced while forcing the pawls outward against the pawl bias springs is found in two steps: 1, summing the moments acting on the pawl about the pawl pivot to find the contact forces between the pawl and the rack, and 2, projecting the resulting normal and frictional contact forces onto the y-axis of the mechanism, along the direction of actuation. The forces and moments acting on the pawl are shown in right-side pawl of Figure 3.6b. The moment, τ, from the pawl bias spring forces the pawl against the rack tooth creating a contact force, $\boldsymbol{F_n}$, normal to the pawl contact surface. A corresponding friction force, $\boldsymbol{F_f}$, acts along the pawl contact surface as the rack slides forward along the surface forcing it outward. Resultant forces (R_x and R_y) create no moment about the pawl pivot such that the moment balance about the pivot, assuming quasi-static motion, is

$$\boldsymbol{C} \times (\boldsymbol{F_f} + \boldsymbol{F_n}) + \tau = 0, \tag{22}$$

where the vector $\boldsymbol{C}$ from the pawl pivot to the contact point is a function of the displacement of the rack from the pawl disengagement kinematics (Equation 19), and the pawl bias spring moment, τ, is in general, a function of the pawl angle, θ_{pawl}.

The normal force, $\boldsymbol{F_n}$, on the pawl is a scalar force, F_n, in the direction of unit normal, $\hat{\boldsymbol{n}}_{\boldsymbol{0}}$, to the contact surface in the fully engaged position ($y_{rack} = 0$) rotated by the pawl angle, θ_{pawl}. Using a standard planar rotation matrix, the normal force is

$$\boldsymbol{F_n} = \begin{bmatrix} \cos\theta_{pawl} & \sin\theta_{pawl} \\ -\sin\theta_{pawl} & \cos\theta_{pawl} \end{bmatrix} \hat{\boldsymbol{n}}_{\boldsymbol{0}} F_n, \tag{23}$$

where the initial unit normal, $\hat{\boldsymbol{n}}_{\boldsymbol{0}}$, is a function of the tooth and pawl geometry expressed as

$$\hat{\boldsymbol{n}}_{\boldsymbol{0}} = \frac{1}{\sqrt{{l_{yd}}^2 + {l_x}^2}} \begin{bmatrix} l_{yd} \\ l_x \end{bmatrix}. \tag{24}$$

The friction force, $\boldsymbol{F_f}$, is found by rotating $\boldsymbol{F_n}$ by 90 degrees counter-clockwise and scaling by a Coulomb friction coefficient, μ, yielding

$$\boldsymbol{F_f} = \begin{bmatrix} 0 & -1 \\ 1 & 0 \end{bmatrix} \begin{bmatrix} \cos\theta_{pawl} & \sin\theta_{pawl} \\ -\sin\theta_{pawl} & \cos\theta_{pawl} \end{bmatrix} \widehat{\boldsymbol{n}}_{\boldsymbol{0}} F_n \mu. \tag{25}$$

These normal and friction forces are determined by substituting their expressions (Equations 23 and 25) into the moment balance (Equation 22). Using the pawl disengagement kinematics (Equation 19) for the pawl angle, θ_{pawl}, in terms of the rack displacement, y_{rack}, and solving the moment balance for the scalar normal force, F_n, yields

$$F_n = \frac{-\tau}{\sin(\gamma)\left(C_{x_0}\mu - y_{rack} - C_{y_0}\right) + \cos(\gamma)\left(\mu\left(y_{rack} + C_{y_0}\right) + C_{x_0}\right)} \tag{26}$$

where**,**

$$\gamma = \theta_{pawl} + \tan^{-1}\left(\frac{l_{yd}}{l_x}\right), \tag{27}$$

$$C_{x_0} = l_x - t_x, \tag{28}$$

and

$$C_{y_0} = t_y - l_{yr}. \tag{29}$$

The force applied by the actuation system to displace the rack while disengaging the pawls, $F_{ratchet}$, is computed from this resulting expression for the normal force and the corresponding friction force by projecting sum of the friction and normal force vectors, $\boldsymbol{F_f}$ and $\boldsymbol{F_n}$, onto the positive y-axis where

$$F_{ratchet} = [0 \quad 1]\left(\boldsymbol{F_n} + \boldsymbol{F_f}\right). \tag{30}$$

This expression provides the required ratchet force which is used in the design of the actuation system following the Reset View methodology.

3.3. Prototype

The specified components, fabrication, and assembly of the ratcheting mechanism and data acquisition and control system are presented here. To realize a design for the SMA actuator and reset spring of the ratcheting mechanism, the Reset View Design Methodology developed in section 3.2.1 was applied. However, prior to applying the Reset View Design Methodology, the

experimental determination of a safe range of applied tensile loads was conducted to determine the value of F_{bowel}. The ratcheting mechanism and other components were fabricated both by traditional milling and by rapid prototyping with a Stereolithography machine. The electronics of the data acquisition and control system were manually soldered onto custom printed circuit boards manufactured by a commercial board house.

3.3.1. Determination of Safe Applied Bowel Tension Range

The specification of F_{bowel}, the operating load against which the ratcheting mechanism should extend, is governed by the range of tensile loads that may safely be applied to porcine small bowel tissue to induce its growth. Although important for the design of the ratcheting mechanism, the knowledge of the safe range of tensile loads is also important to maintain the health of the pigs in which the devices are implanted. The two main health risks involved in the application of tensile load on the small bowel are 1) damage due to tissue ischemia caused by the constriction of blood vessels of the tensioned bowel tissue or mesentery, and 2) damage due to tissue tearing or severe tissue disruption. To establish the upper bound of the safe loading range, *in vivo* and *ex vivo* tensile loading experiments were performed and are summarized in this section. For greater detail, please refer to Miyasaka, *et al* [12].

3.3.1.1. Acute *In Vivo* Testing of Ischemic Failure Limit

To evaluate the tensile loads that lead to bowel and mesentery ischemia, segments of bowel tissue were tensioned in vivo by an early design iteration of the Instrumented SMA Driven Ratchet. The experiments were conducted *in vivo* because their goal was to evaluate the change in blood flow within the bowel and mesentery as the applied tension to the bowel was increased. The segments of bowel were tensioned to approximately 30, 60, 90, 120, 160 and 200 gf by a previous bowel extending device. The velocity of the blood flow was evaluated using a laser Doppler imaging system, shown in Figure 3.8, which scanned the tensioned tissue at each of the aforementioned magnitudes of tension.

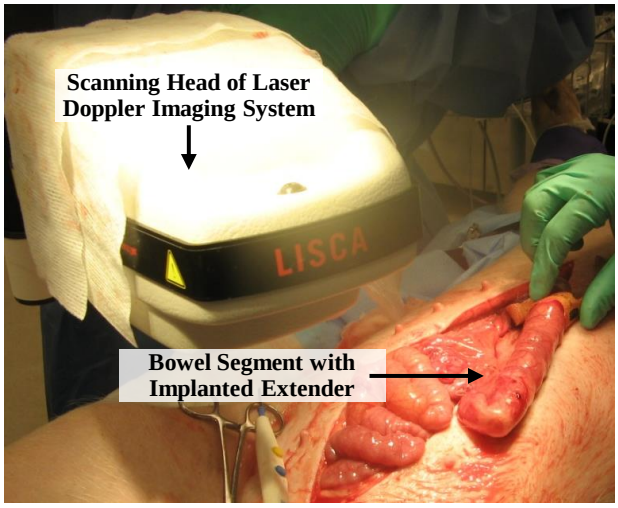


Figure 3.9. *In Vivo* Tensile Loading Setup.
Small bowel segments were tensioned by the Instrumented SMA Driven Ratchet. As the applied tension was increased, a laser Doppler imaging system was used to determine the velocity of blood flow in the mesentery and small bowel.

Results from the experiment indicate that blood flow was present within the mesentery for all of the applied loads, but the blood flow within the bowel tissue was partially restricted at approximately 90 gf, and completely stopped at 120 gf. The area of tissue which became acutely ischemic during the experiments is where the end of the pushrod abutted the tissue, compressing it. The risk of bowel ischemia is that the tissue may become necrotic, or dead, which could cause the weakened bowel tissue to rupture, allowing the enteral contents of the isolated bowel segment into the abdomen. Thus, the study recommended an upper limit on the applied load of 90 gf.

3.3.1.2. *Ex Vivo* Testing of Mechanical Failure Limit

To evaluate the tensile loads that lead to bowel tearing and/or the onset of severe tissue disruption, a series of *ex vivo* tensile load experiments were performed. With the experimental setup shown in Figure 3.10, tensile load was applied to segments of small bowel tissue (with the mesentery intact) excised from a pig. Load was transferred to the tissue, which was submerged in a 40°C 0.9% saline bath to best mimic physiological conditions, by a string passing through two pulleys with a weight attached to one end. The bowel segments ranged from 10 to 15 cm in length, and were attached to the edge of the saline bath and to the string by plastic adaptors on which the bowel was sutured. The applied load was increased from 0 gf to 1 kgf, or until tissue failure, by

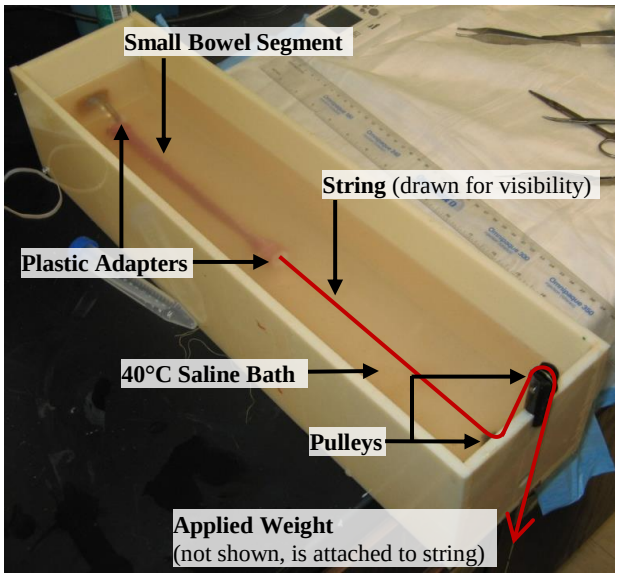


Figure 3.10. ***Ex Vivo* Experimentation Setup**.
Small bowel segments were submerged in 40°C saline, and tensioned with dead weights attached to a string through a system of two pulleys to determine the applied bowel tensions associated with mechanical tissue damage.

increments of 20-40 gf every two minutes. After each segment of bowel tissue was tensioned, tissue samples were taken for histological review.

Over the six trials of the experiment, the results had significant variation. Three segments of bowel tissue withstood up to 1 kgf, the upper limit specified by the experimental protocol, without tearing. In one segment, the mesentery of the bowel tore at 235 gf. In the remaining two segments, the bowel wall failed at 515 gf and 595 gf. While the maximum load that the bowel and mesentery could withstand without damage varied from 235gf to 1kgf, all of these tests resulted in applied loads which significantly exceeded the recommend load of 90gf from the *in vivo* experiments. Thus, it is clear that risk of bowel ischemia is the limiting factor on the range of loads that may safely be applied to the bowel tissue. To reduce the chance of health complications associated with loading the bowel, an upper limit on the applied load of 90 gf was determined.

3.3.2. Application of Reset View Design Methodology

Using the Reset View methodology outlined in Section 3.2.1 to design the actuation of the Instrumented SMA Driven Ratchet involves the transformation of the SMA stress-strain curves into the force-displacement space of the reset spring using the diameter and length of the SMA

wires as well as the system forces ${F_{sys}}^{A}$ and ${F_{sys}}^{M}$. The system forces are composed of the ratchet force, $F_{ratchet}$, derived from the model in Section 3.2.2.2, the force to be applied to the bowel, F_{bowel}, bounded in Section 3.3.1, the friction force, $F_{friction}$, between the sliding components within the device that was conservatively estimated, and the force required to slide the pushrod through the seal, F_{seal}, which was measured experimentally. The design process is presented in five steps: 1) define the geometric parameters of the pawl and rack, 2) predict the loads, excluding the contribution of the reset spring, experienced by the SMA wire in its austenite and martensite phases to specify the shifting transformations of the material curves into the Reset View, 3) determine candidate SMA wire diameters and length based on these forces and the device package size, 4) select the maximum operating stress of the wire and desired stroke, and 5) use the resulting motion limits with the transformed SMA curves in the Reset View to determine the feasibility of each SMA wire diameter and the corresponding maximum reset spring stiffness.

The first step of the Instrumented SMA Driven Ratchet design was to select ratchet pawl and rack parameters which are driven by the packaging, stepping, and load bearing constraints presented in the tooth and pawl geometric model in Section 3.2.2. In this porcine case study, the ratcheting mechanism of the device was constrained to fit within a case with a wall thickness, t_{case}, of 0.03 inches and an 11/16 inch outer diameter sized to fit within the 0.75 inch diameter bowel lumen, d_{bowel}. The tooth and pawl geometries were limited by the packaging constraint from Equation 9. To safely regulate the extension and force applied to the bowel, a small step size, $\delta_p = l_{yr} + l_{yd}$, of 0.05 inches was selected. The design of the tooth and pawl geometries was guided by this step size, the requirement of full-skip reengagement (Equation 12), which implies the self-locking condition (Equation 10), and an FEM-based stress analysis to ensure that the ratchet can safely bear a 5 lb load (well above the forces required by the application). The resulting geometric parameters are listed in Table 3.1.

Table 3.1. Geometric Parameters of Pawl and Pushrod

t_x	0.1027 in
t_y	0.0834 in
l_{yd}	0.0234 in
l_{yr}	0.0234 in
l_x	0.0261 in
w_x	0.0757 in
d_{rod}	0.1200 in

The second step of the design process was to predict the forces which define the shifting transformations into the Reset View. A maximum bowel force, F_{bowel}, of 90 gf was obtained from the *ex vivo* and *in vivo* bowel tension tests described in *Section 6*, which was doubled for robustness purposes in the design. The friction force from the sliding components of the device, $F_{friction}$, was conservatively estimated as 100 gf. The seal force, F_{seal}, was measured to be approximately 150 gf by pushing a 0.14 inch diameter threaded rod of a similar diameter and tooth pitch to the designed pushrod through a 1/16 inch hole punched in a 3/16 inch thick sheet of Viton® foam seal material. To compute the peak force to disengage the ratchet, $F_{ratchet}$, the pawl bias spring torque, τ, was measured as 0.00285 lbf-inch/deg with a pre-load of 0.0064 lbf-inch in the fully engaged position by bending the superelastic SMA wire springs through small angles with a load cell. Using the rack and pawl geometric parameters given in Table 3.1, Equation 30 of the ratcheting model described in Section 3.2.2 was used to calculate the peak force experienced by the SMA wire due to the interaction of the rack and pawls as 120 gf (60 gf per disengaging pawl). These forces define the scaling transformations for the Reset View, where the austenite curve is shifted downward by ${F_{SYS}}^{A}$=220 gf (0.49 lbf), and the martensite curve is shifted upward by ${F_{SYS}}^{M}$=550 gf (1.21 lbf).

The third step was to use these forces along with the packaging constraints of the device to compute the lower bound of the SMA wire diameter, d_{min}, and its length. The dimensions provide the scaling transformations from stress and strain to force and displacement in the Reset View. A minimum wire diameter of 6.4 mil was determined from Equation 5 from which the next two larger commercially available candidate wire diameters were selected as 8 mil and 10 mil. Stress-strain curves for 8 mil diameter 70°C Flexinol® wire were determined experimentally by heating and cooling a segment of wire tensioned by an increasingly heavy dead load, the results of which were applied to both the 8 mil and 10 mil cases. While the maximum initial length of the device was specified as 6.5 inches, the length of the two parallel segments of SMA actuator wires was limited to 3.63 inches because of the space required for the sensing, the circular bowel attachment, and sealing components. This length and the candidate SMA wire diameters (8 and 10 mil) define the scaling from stress-strain to force-displacement, which combined with the previously determined system load shifts, ${F_{sys}}^{A}$ and ${F_{sys}}^{M}$, fully define the transformation into Reset View which is plotted in Figure 9 for each candidate wire diameter.

The fourth step of the design process was to select the maximum operating stress and desired stroke of the SMA wire which defines the hard stop location. A maximum stress on the wire of 180 MPa was selected from the manufacturer's specifications, which translates to a net maximum SMA force of 2.62 lbf and 4.10 lbf for the 8 and 10 mil cases which are transformed and plotted as horizontal lines on the Reset View plots (Figure 3.11). A desired stroke, δ, was conservatively set as 0.145 inches, which is just over three times the 3/64 inch tooth pitch, δ_p. This sets the hard stop location at 0.155 inches, which is defined by the location of the intersection between the transformed austenite curve and the transformed maximum SMA force line shifted by the 0.145 inch desired stroke (point labeled **A** and marked with a vertical line in Figures 9a and 9b at 0.01 inches).

The fifth design step is to use these stroke limits and the transformed SMA curves to determine the maximum allowable reset spring stiffness, k_{max}. The intersection between the hard stop vertical line and the transformed martensite curve (point labeled **B** in Figures 9a and b), along with the maximum SMA force intersection at **A**, define the maximum allowable spring constant, k_{max}, as described by Equation 7. For the wire diameters of 8 and 10 mil, the maximum values of the reset spring constants were 0.7 lbf/in and 7.5 lbf/in, respectively. The 8 mil wire is capable of providing the desired force and stroke, but with very little force available for design adjustment and robustness. In addition, compression springs capable of producing the required forces are generally not available with such a low stiffness. Therefore, the 10 mil wire diameter was chosen to allow a range of design adjustments, and for which a wide variety of rest springs is available that satisfy the 7.5 lbf/in maximum spring stiffness limit. Softer springs are also feasible depending on the variety of commercially available springs and the packaging limits of the device, and the Reset View enables the visualization of the performance and robustness implications for alternate (more compliant) spring selections.

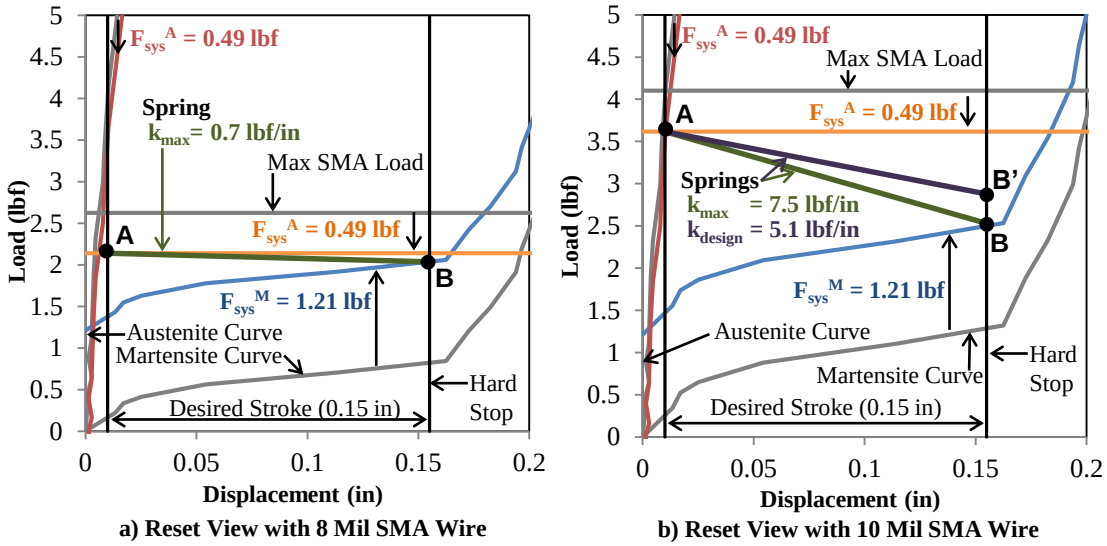


Figure 3.11. Reset View Design of Actuator with 8 and 10 mil SMA Wire.

The Reset View Design Methodology is applied to the design of the bowel extender for two SMA diameters. In the 8 mil design, a spring constant less than or equal to 0.7 lbf/in (0.12 N/mm) was required to achieve the desired stroke. A commercially available spring with a lower or equal spring stiffness designed for the operating loads (approximately 2 lbf) could not be specified. In the 10 mil design, the spring constant must be equal to or less than 7.5 lbf/in (1.3 N/mm) to achieve to same desired stroke. In the final design, the 10 mil SMA wire was chosen because many commercially available springs could be selected to meet the design, and a spring with a stiffness of 5.1 lbf/in (0.9 N/mm) was specified.

3.3.3. Ratcheting Mechanism Prototype

The ratcheting mechanism was assembled mostly of components fabricated by the Viper™ SLA® rapid prototyping system from 3D systems, from a propriety material called Accura 60. The rapid prototyped components, which are the translucent parts shown in Figure 3.12d, include the ratchet pawls (4x), the outer casing, the end cap, the circular attachment, and the rear and front housing. The pawl bias springs (4x), are 0.175 in long segments of 15 mil diameter superelastic SMA mounted to the rear and front housing with epoxy. The pushrod is a circular rack machined from a 0.1875 diameter stainless steel rod using a 60 degree angle cutting drill-mill to create the angular grooves. The pushrod attachment was machined from Delrin, and given holes for allowing the passage of enteral contents. To seal the device from enteral contents, the outer casing, circular

attachment, and end cap are coated with room temperature vulcanizing silicone adhesive, and the pushrod/outer casing interface was sealed with a laser cut annular Viton® seal affixed to the outer casing. The only materials exposed to the enteral contents directly are Delrin (pushrod attachment), stainless steel (pushrod), Viton (pushrod seal), and silicone (encapsulates device body), all of

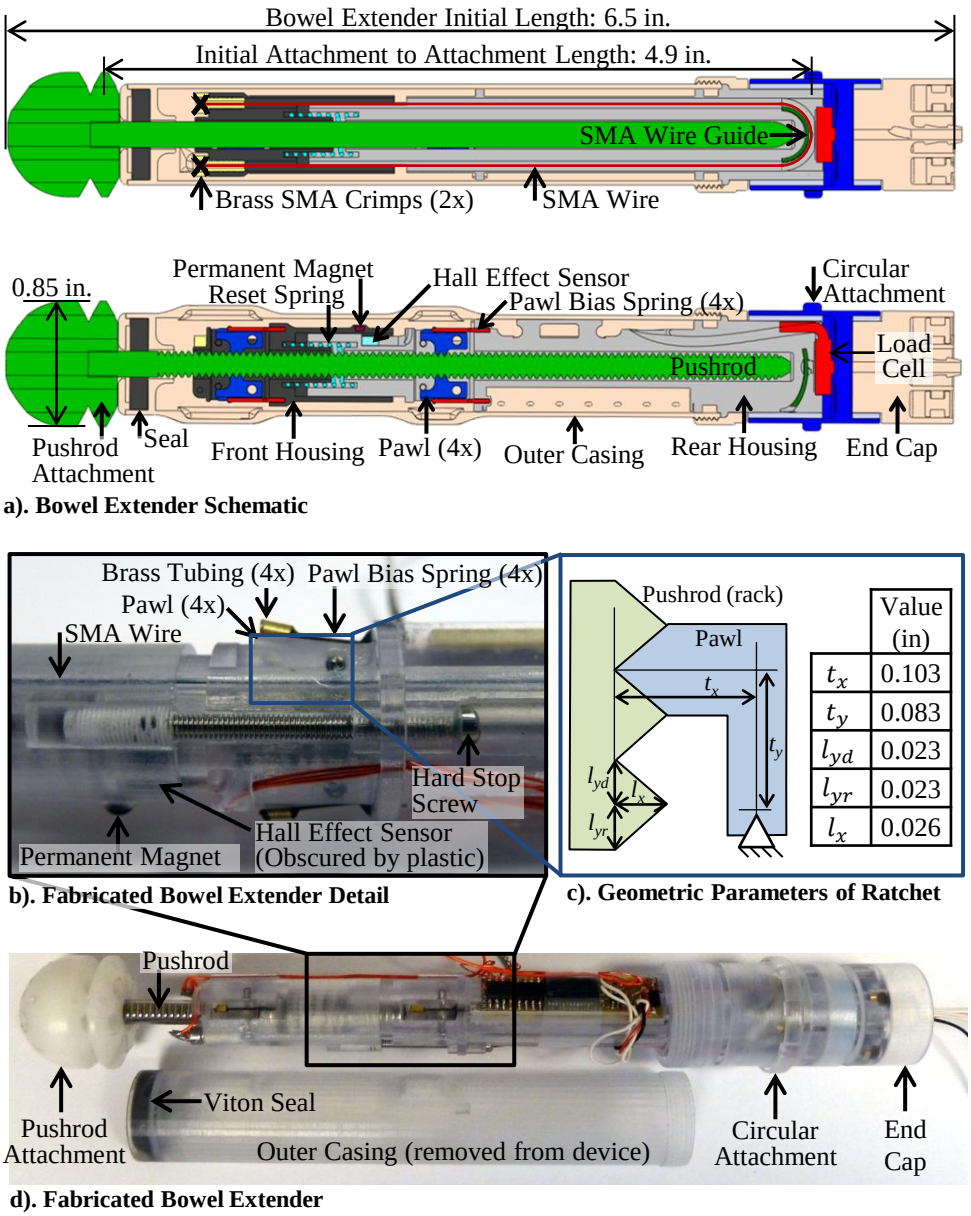


Figure 3.12. Prototype of Instrumented SMA Driven Ratchet.
Schematic section views and photographs display the designed and fabricated Instrumented SMA Driven Ratchet (a). A detailed view (b) shows small components of the ratcheting mechanism, and a diagram of the ratchet pawl and rack (c) defines the important geometric design parameters. Translucent components were fabricated using an SLA printer and all other components were manually fabricated.

which are sufficiently biocompatible for short-term (< 1 month) intraluminal small bowel implantation.

The SMA wire (10 mil Flexinol® wire, Dynalloy) was mounted through two stainless steel vented screws with brass crimps, and routed around a stainless steel SMA guide machined from 3/8 inch outer diameter tubing. The vented screws allowed the SMA wire to be tensioned accurately after installation. To reduce the chance of the SMA wire melting the Accura 60 material, 1/16 inch outer diameter PEEK tubing lines the path taken by the SMA within the device. The SMA is symmetrically routed to eliminate binding between the front flaps and rear housing. The electrical connections to the actuator were made at the stainless steel guide and the two brass crimps, which are electrically connected at the front housing. The reset spring (P/N 70812, from Century Spring) was placed between the front and rear housing and pushes the front housing forward until the Martensite hard stop is engaged, resetting the SMA to the desired Martensite strain.

3.3.4. Data Acquisition and Control System Prototype

The data acquisition and control system comprises the load sensor, displacement sensor, and the three electronic circuits that sample the load and displacement sensors, transmit/receive data to/from the PC interface, and drive the SMA wire actuator. The displacement and force sensors are mounted on the rear housing, as shown in Figure 3.12a. The Hall Effect sensor (SS495, Honeywell) was mounted such that as the front housing is drawn closer to the rear housing, a permanent magnet mounted on the front housing causes an increase in the output of the Hall Effect sensor. The load cell (LPM-510b, Cooper Instruments) is mounted on the end of the rear housing, and its wires are routed through the rear housing to reach the Bowel Extender Circuit. Load is transferred from the circular bowel attachment, which is not rigidly fixed to the rear housing or end cap, to the load cell. The load path to the sensor is not direct due to the presence of the silicone seal, but it was accounted for in the sensor calibration which was performed with the seal in place at a typical internal temperature for a pig (39° C) in a saline bath. External loads on the device that are not caused by the small bowel tissue tension are not measured by the load sensor, because the end cap is rigidly attached to the rear housing with 0-80 stainless steel screws. Thus, the effect on the load sensor output caused by the pig's position and activity is minimized.

To create the Bowel Extender, Pack, and Base Station Circuits, electronic components were selected for each, the layout of each board was designed, custom printed circuit boards were fabricated by a commercial board house, and the components were manually soldered. The components selected for the Instrumented SMA Driven Ratchet electronics are shown in Table 3.2 The choice of specific components was driven largely by the need to minimize power consumption

Table 3.2. Data Acquisition and Control System Components.
Component selection for the Pack and Bowel Extender Circuits was driven by the need to minimize power consumption and circuit size. The Base Station circuit is not designed for implantation and thus through-hole components were selected for their ease of soldering. Furthermore, because the Base Station Circuit is battery powered, the power consumption of its components was not a design driver.

Circuit	Component	Manufacturer	Model	Package	Label in Fig. 6
Base Station and Pack Circuit	433 MHz Wireless Transceiver	Nordic Semiconductor	nRF905	32 Pin QFN	1
Bowel Extender and Pack Circuit	Voltage Regulator (2.7 Volts)	Analog Devices	ADP3300	6 Pin SOT 23	2
	Microcontroller	Microchip	PIC16F886	28 Pin DIP	3b
Base Station Circuit	Microcontroller	Microchip	PIC16F886	28 Pin SSOP	3a
	Voltage Regulator (3.6 Volts)	Linear Technology	LT1086	3 Pin TO-220	4
	Voltage Regulator (5 Volts)	Texas Instruments	TL750L	3 Pin TO-220	5
	Line Driver/Receiver	Texas Instruments	MAX232N	16 Pin DIP	6
	Optical Isolators	TT Electronics	OPI1264	~	7
Bowel Extender Circuit	Power MOSFET	ON Semiconductor	NTHD3100C	6 Pin TSOP	8
	Digital Potentiometer	Analog Devices	8400ARZ1	8 Pin SOIC	9
	Instrumentation Amplifier	Burr Brown	INA 122	8 Pin SOIC	10

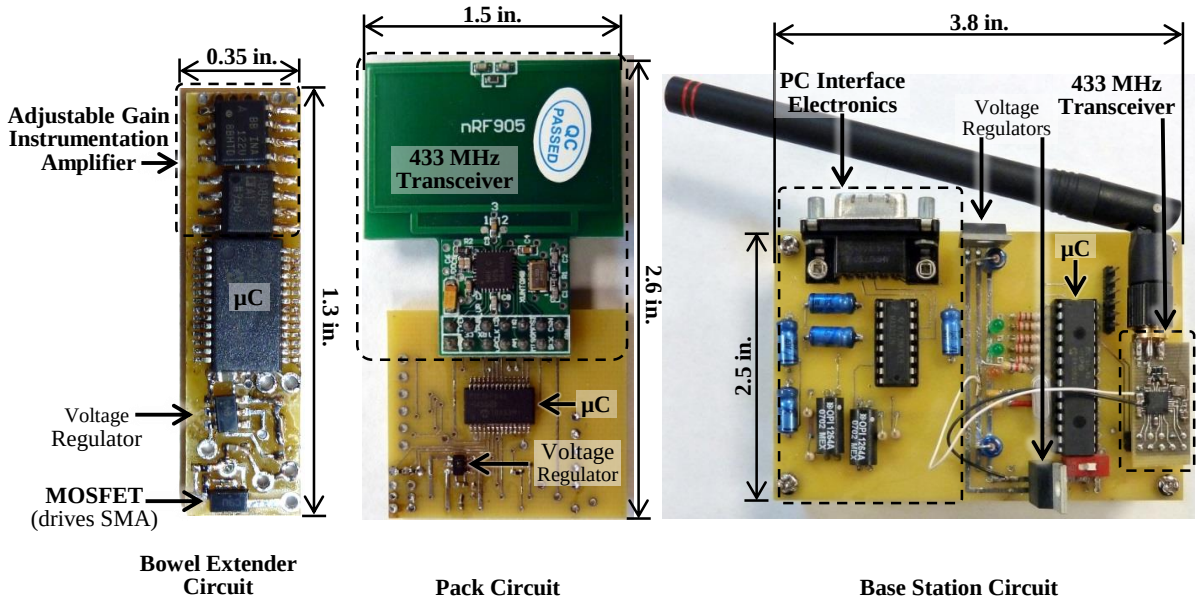


Figure 3.13. Data Acquisition and Control System Prototype.
The tan printed circuit boards of the three circuits comprising the data acquisition and control system prototype were manufactured at a commercial board house and all components were manually soldered. Surface mount components were used to minimize the size of the implanted electronic circuits.

and footprint size for both the Bowel Extender Circuit and Pack Circuit. Because the Base Station Circuit is not implanted, size and power considerations were not important and those components were selected based solely on their functionality. Photographs of each circuit (Figure 3.13) show the layout of components and the overall circuit dimension. The Bowel Extender Circuit and Pack Circuit are powered by a lithium battery (Tadiran, TLM-1530MP) with a 340 mAh capacity and the ability to source a current pulse of up 5 amps, which is more than sufficient to drive the 1.05 Amps (Dynalloy specification) required to heat the SMA wire.

3.4. Benchtop Validation

The ratcheting force model developed in 3.2.2.2 was evaluated to determine its accuracy and to make adjustments to the SMA wire diameter and/or reset spring design if necessary. The performance of the ratcheting mechanism and data acquisition and control subsystems were successfully validated as separate subsystems on the benchtop, and as an integrated full system in a two-week submersion experiment developed to mimic basic aspects of the operating environment with a living pig.

3.4.1. Ratchet Model Validation

The success of the SMA wire and reset spring design hinges on the accuracy of the predicted system loads on the SMA wire during the operation of the ratcheting mechanism. Thus, the system load curves of the Instrumented SMA Driven Ratchet prototype were experimentally measured by mimicking the action of the SMA wires with steel cables attached to a load transducer and measuring the displacement of the front housing relative to the rear housing with a displacement sensor. To validate the ratcheting force model, the experimental data are compared with the predicative model that incorporates the axial components of the load caused by the interaction of the rack and pawl, the friction of the front and rear housing, and the reset spring.

3.4.1.1. Ratcheting Force Model Validation Setup

The forces acting on the SMA wire within the mechanism were measured using the experimental setup shown in Figure 3.14. In this setup, the SMA wires in the Instrumented SMA Driven Ratchet device (with the seal removed) were replaced with steel cables attached to a linear motion stage through a load cell to induce motion, emulating the action of the SMA wires, while measuring the corresponding force. The displacement of the front housing relative to the rear

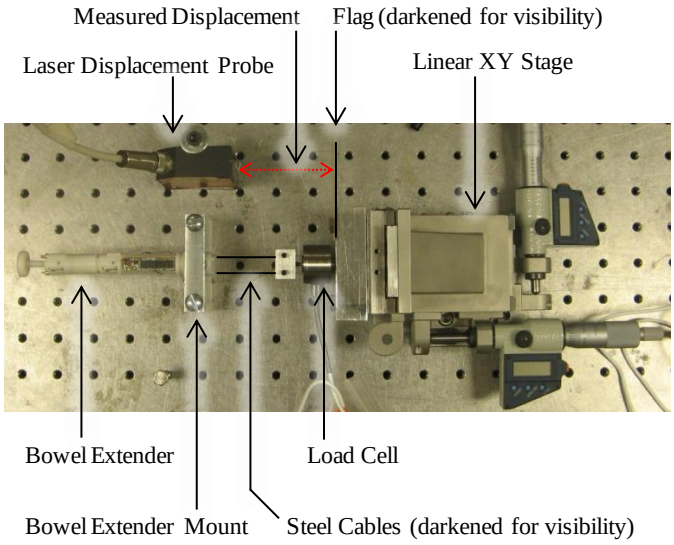


Figure 3.14. Experimental Setup.
To measure the load experienced by the SMA during normal operation, the SMA wire was replaced by two steel wires connected to a load cell fixed to a linear stage. As the linear stage was translated back and forth, the action of the SMA was mimicked by the steel wires. The motion of the mechanism was captured by a laser displacement probe.

housing was simultaneously measured with a laser displacement probe. The force-displacement cycle were recorded from the load cell and laser displacement probe by a National Instruments data acquisition board (NI USB-6009) and LabVIEW.

3.4.1.2. Ratcheting Force Model Validation Procedure

Starting with the mechanism in the initial state with the reset spring forcing the front housing against the hard stop and the rear pawls fully engaged, the linear stage was slowly advanced, pulling the front housing back a total distance of 0.055 inches (slightly more than the 0.05 in rack pitch) emulating heating of the SMA wires. The linear stage was then slowly returned to its initial position, emulating cooling of the SMA wires.

3.4.1.3. Ratcheting Force Model Validation Results

The collected data are plotted in Figure 3.15 against the combined predicted forces from the spring, F_{spring}, given its 5.1 lbf/in spring constant, the measured sliding friction in the device, $F_{friction}$, and the ratcheting force, $F_{ratchet}$, as computed in Equation 30 from the ratchet force model. In Figure 3.15, the transitions of the ratcheting mechanism are labeled, corresponding with the labels in Figure 3.16, which shows the path of the tip of the front pawls during disengagement.

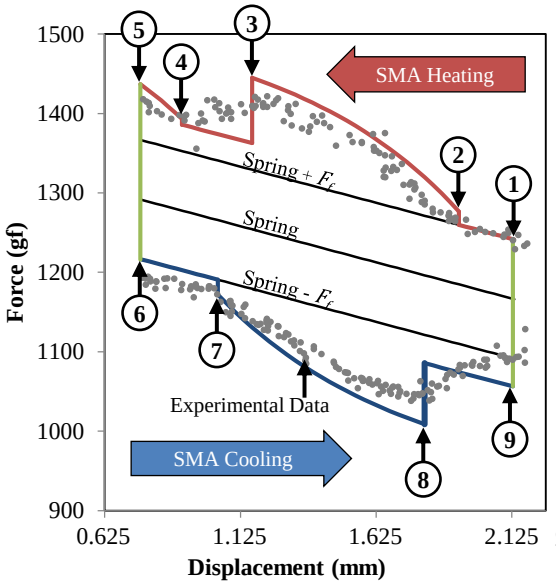


Figure 3.15. Experimental Force-Displacement Results.
The experimental data are plotted against the predictive model of the ratchet rack/pawl force interaction. The force displacement curve follows a sequence through the labeled points 1-5 as the SMA heats (red curves), and a similar sequence 6-9 as the SMA cools (blue curves). Overall, the agreement is strong, validating of the ratchet force model.

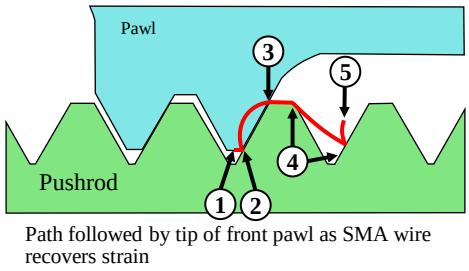


Figure 3.16. Path Followed by Tip of Pawl.
The path followed by the tip of the pawls is shown, for clarity, with numbered labels that correspond with those in Figure 3.15. The path is drawn for a stationary pushrod while the pawl is pulled to the right by the SMA actuator as it heats.

From ① to ②, the steel cables begin pulling the front housing toward the rear housing, mimicking the action of the SMA. In this interval, the front pawls have not yet engaged the rack due to a 0.01 inch backlash present between the two pawl sets. In this condition, there is no ratchet force and the wires act against the superposition of the spring and frictional loads only, as shown by the sloped line connecting points ① and ② in both the force deflection plot (Figure 3.15) and the pawl tip path (Figure 3.16). Since the value of the sliding friction, $F_{friction}$, in the device was

conservatively estimated at 100 gf, the shift of the measured force-displacement data from the spring line was used to adjust this estimate where the actual friction in the device was 75 gf. The over estimation of $F_{friction}$ provides the ratcheting mechanism with an additional 25gf of actuation capacity against external loads, and simultaneously reduces the maximum operating load subjected to the SMA wires by 25 gf. With this adjustment, the measured data exactly follow the spring and friction prediction (within measurement noise), demonstrating the accuracy of these predictions.

At point ②, the front pawls make contact with the face of the pushrod tooth, and from ② to ③, the front pawls rotate outward against the pawl bias springs. In this interval, the spring and friction forces combine with the ratchet force, $F_{ratchet}$, as predicted by Equation 30 as a function of the rack displacement, y_{rack}. Within this interval, the forces increase with decreasing slope as the pawl bias springs are bent and the pawl rises up the face of the tooth, with a small discontinuity when the pawl first contacts the rack to overcome the preload in the bias spring. Both the model and the experimental data exhibit this general qualitative trend, although the discontinuity is not pronounced in the experimental data due to compliance in the components that was not modeled. The total magnitude of the rise in force over the friction and spring load was measured to be 90 gf, which is only 22% lower than the model prediction even though many of the components and resulting motions were fabricated near the 0.004 inch precision limit of the rapid prototyping machine. The accuracy of this prediction is critical as it provides the peak ratchet force, $F_{ratchet}$, used in the Reset View methodology.

From point ③ to ④, the pawl tooth slides along the flattened tooth tip of the rack (not represented in the analytical model), as shown in Figure 3.16. In this interval, the ratchet force is no longer active since the pawl does not disengage further against the bias spring but rather maintains a constant angle. Instead, in addition to the device friction and spring forces, a friction force is generated between the pawl tip and the flat of the rack tooth due to the inward force, F_n, produced by the pawl bias spring. A Coulomb model is used for this additional friction force, $\tilde{F}_f$, such that

$$\tilde{F}_f = \mu F_n, \tag{31}$$

where μ is the coefficient of friction experimentally measured for the Accura 60 material as 0.17. This friction force is constant over the flat of the rack tooth which adds to the constant device friction and the slope of the spring line in Figure 3.15. In this region, the experimental data does

not follow this shifted sloped line from ③ to ④, but rather follows a downward slope back towards the spring plus friction line due to compliance in the mechanism and due to the fact that the corners of the ratchet components are slightly rounded.

At point ④, the pawl tip skips from the flat, and engages the next tooth of the pushrod as specified by the design of the tooth and pawl geometry. From ④ to ⑤, the continued motion of the linear stage causes the pawl to rise up the face of the next rack tooth, producing a force-displacement curve similar to that from point ② to ③, with further compression (and increased force) on the reset spring. At ⑤, the direction of motion, and thus the sliding device friction, is reversed, subtracting rather than adding to the spring force, and the process repeats as the rear pawls rather than the front pawls rotate away from the pushrod and the devices extends one tooth width (3/64 inch). As the mechanism resets to the initial state (emulating cooling of the SMA), the force due to the interaction of the rear pawls and pushrod reduces the load on the SMA, as shown in Figure 3.15 and predicated by Equation 2.

The values of F_{spring}, $F_{ratchet}$, and $F_{friction}$ were predicted very near or slightly over the actual measured forces, validating the ability of the ratchet force model to provide a useful prediction for the actuation system design using the Reset View methodology. With the model and the methodology, a wide variety of compact SMA driven ratcheting devices can be designed. The design was conservative because the designed strain was 4%, although less than 2% was necessary. The external load against which the device must actuate was doubled in the design, and the predictions of $F_{ratchet}$ and $F_{friction}$ were slightly over predicted. These conservative design measures suggested using a reset spring with a spring constant equal to or less than 7.5 lbf/in, although a spring with a constant of 5.1 lbf/in was selected, adding yet another layer of safety to the design. Such a conservative design was pursued because the targeted operating environment of the Instrumented SMA Driven Ratchet is within the bowel of a living pig, where it must be robust against difficult to estimate external loading conditions and the possibility of biological fluids leaking onto the mechanism.

3.4.2. Ratcheting Mechanism Performance Demonstration

The validated model provides a means for predicting the internal forces of the mechanism that the actuation system must overcome, providing the basis for the Reset View methodology. The performance of the entire device, including the designed actuation system, was experimentally

validated for its ability to actuate against a load and to demonstrate the functionality of the entire device.

The prototype was designed to successfully lengthen against at least the maximum force expected to the applied to the small bowel tissue, F_{bowel}, of 90 gf. In addition to this required load, additional capacity was designed into the device in the form of an extra 90 gf external load specification, a lower spring constant, providing an additional 160 gf (0.35 lbf), an over predicted friction force of 25 gf, and a 25 gf over prediction of the ratcheting force model, for a total of 320 gf of additional load capacity. Furthermore, a lubricant was added to the seal, which was not used in the model validation, that significantly reduced the seal force, F_{seal}, from its measured 150 gf value. Moreover, the desired stroke was also extremely conservative, exceeding the required stroke by a factor of approximately three. Since the SMA wire need not be fully heated to austenite to take a step, this allows additional pre-compression on the reset spring without over-stressing the austenitic wire such that the spring line in the Reset View plot (Figure 9b) could be raised if needed to provide additional force capacity along the hard stop, and consequently against an external load.

To demonstrate the ability of the device to extend against loads well beyond the design requirement, the device was positioned vertically with the pushrod pointing upward. Successive loads in increments of 100 gf were applied to the device by placing weights on the end of the pushrod. The mechanism was actuated under control of the LabVIEW interface in communication with the device over the wireless communication link to evaluate if the entire operation cycle could complete under the load. The Instrumented SMA Driven Ratchet successfully took steps under wireless control against all loads up to and including 800 gf, which is well beyond the design bowel load specification of 90 gf, and also well beyond the additional 320 gf load available from the specifically quantifiable extra load capacity designed into the actuation system. At 900 gf, the extender could not complete the entire operation because the reset spring was unable to expand against the combination of the system load, ${F_{sys}}^{M}$, and the martensitic wire reset force, ${F_{SMA}}^{M}$. The weight was reduced to 850 gf, against which the mechanism could reliably actuate.

Although the force the mechanism can produce is much higher than the safe loading limit on the bowel of 90 gf, the additional load capacity may be needed to overcome difficult to predict forces acting on the Instrumented SMA Driven Ratchet while implanted that depend on the pig's activity, position and size. The additional force capability of the device does not present a risk to

the health of the pig, because the load applied directly to the bowel is measured at the point of attachment, allowing medical personnel to stop lengthening the device if the bowel tension nears the 90 gf limit. Furthermore, because the extension of the device per actuation is small (1.2 mm), reliable, and controlled, the risk of applying excessive bowel tension is minimal. Thus, this full system demonstration validates the ability of the device to safely actuate against the bowel tissue loads and against much larger additional loads acting through the body of the pig.

3.4.3. Data Acquisition and Control System Performance Demonstration

The load sensor was calibrated to determine its range and resolution, and the displacement sensor output corresponding to a successful actuation was determined. To calibrate the load sensor, the Instrumented SMA Driven Ratchet was mounted vertically within a saline bath held at pig temperature, 39°C, by an environmental chamber. After allowing the temperature of the Instrumented SMA Driven Ratchet to equilibrate, 20gf dead weights were sequentially added up to 180 gf and then subsequently removed. The output of the load sensor was linear within the range of weights used for the calibration, with a resolution of approximately 2.25 gf and a measurement range of 0 to 1.75 kgf, assuming linearity of the output beyond 180 gf. The displacement sensor output associated with a successful step was measured by manually actuating the ratcheting mechanism with the minimum distance required while recording the output of the Hall Effect sensor.

Using a logic analyzer and a current sensor, the operation of the data acquisition and control system was validated and the communication content and timing were fine tuned to reduce the power consumption of the system when the Pack Circuit and Base Station Circuit are both out of and in the range of the wireless communication link. Because of the expected signal attenuation of the tissue, the range of the wireless communication link was experimentally measured with a cadaveric pig model by placing the Pack Circuit within its abdominal cavity, closing the midline incision, and slowing distancing the Base Station Circuit until the flow of communication became unreliable. The experimentally determined range was approximately 5 meters, which is more than necessary considering the size of the animal model's cage.

3.4.4. Benchtop Environmental Validation

To check the Instrumented SMA Driven Ratchet seals and validate its performance when submerged in a reasonable approximation of the fluidic environment of the small bowel, the

Instrumented SMA Driven Ratchet was placed in a 39°C saline bath for 2 weeks, the maximum expected length of an *in vivo* experimental study. The submersion experiment was also used to verify the sufficient lifetime of the battery by actuating the device following a typical expansion protocol. After two weeks of submersion, no leakage into the device was observed, the battery capacity remained high, and no corrosion or other material change was evident.

Although the benchtop experiments were successful, many aspects of the *in vivo* environment could not be well replicated without significant effort. These factors include the loading environment, the pressure and composition of fluids surrounding the Instrumented SMA Driven Ratchet, and the biological reaction of the porcine model to the Instrumented SMA Driven Ratchet. The benchtop results were encouraging, but ultimately, the conclusive performance validation of the Instrumented SMA Driven Ratchet was achieved through *in vivo* experimentation.

3.5. *In Vivo* Experimental Studies

To demonstrate the versatility of the integrated prototype, evaluate its *in vivo* performance, induce functional and healthy longitudinal porcine bowel growth, and observe the response of the bowel tissue to displacement-based and load-based expansion approaches, three *in vivo* experiments utilizing the Instrumented SMA Driven Ratchet were conducted. During the three implantations, displacement and load data were recorded, and on the eighth post-operative day, the Instrumented SMA Driven Ratchet was removed and tissue samples were taken to evaluate the health and functionality of the growth tissue segments. To demonstrate the versatility of the Instrumented SMA Driven Ratchet and its potential for enabling new medical studies, three expansion approaches were explored: constant rate impulsive displacement control, displacement rate limited load control, and constant load control.

3.5.1. Experimental Procedure

The experimental procedure consists of three distinct phases: surgical implantation, ratcheting mechanism expansion, and tissue evaluation. The experiments described herein were approved by the University Committee on Use and Care of Animals at the University of Michigan (Protocol #09026).

3.5.1.1. Surgical Implantation and Tissue Analyses

A surgical implantation procedure was developed to implant the Instrumented SMA Driven Ratchet intraluminally, but not within the continuous GI tract. Rather, the device was implanted within a Roux limb connecting the continuous GI tract to a stoma located on the underside of the porcine model. The surgery began with a 15 cm midline incision to open the abdominal cavity of the porcine model. The small bowel was manipulated to determine the flow direction of enteral contents, and to locate the Ligament of Treitz, which marks the start of the small intestine. Approximately 90 cm along the length of small bowel from the Ligament of Treitz the small bowel was cut, creating two open ends of bowel labeled (a) and (b), as shown in Figure 3.16. Approximately 90 cm along the length of bowel from (b), an end-to-side anastomosis was created, connecting (a) to (c) and restoring the continuity of the GI tract. The segment of small bowel from (b) to (c), or Roux limb, was no longer in the continuity of the GI tract and would not pass ingested contents, however, the health of the Roux limb was maintained by the blood supply from the intact mesentery. During the creation of the Roux limb, the Instrumented SMA Driven Ratchet was sterilized by soaking it in a liquid sterilant (Metrix, Metricide®) for the manufacturer recommend time of 40 minutes. After sterilization, the device was thoroughly rinsed with sterile saline to prevent any sterilant from getting into the surgical field. The Instrumented SMA Driven Ratchet was inserted, pushrod end first, into the open end of the Roux limb, and was sutured in place with the device-to-tissue attachments. A stoma, or surgically created opening, was made in the skin and

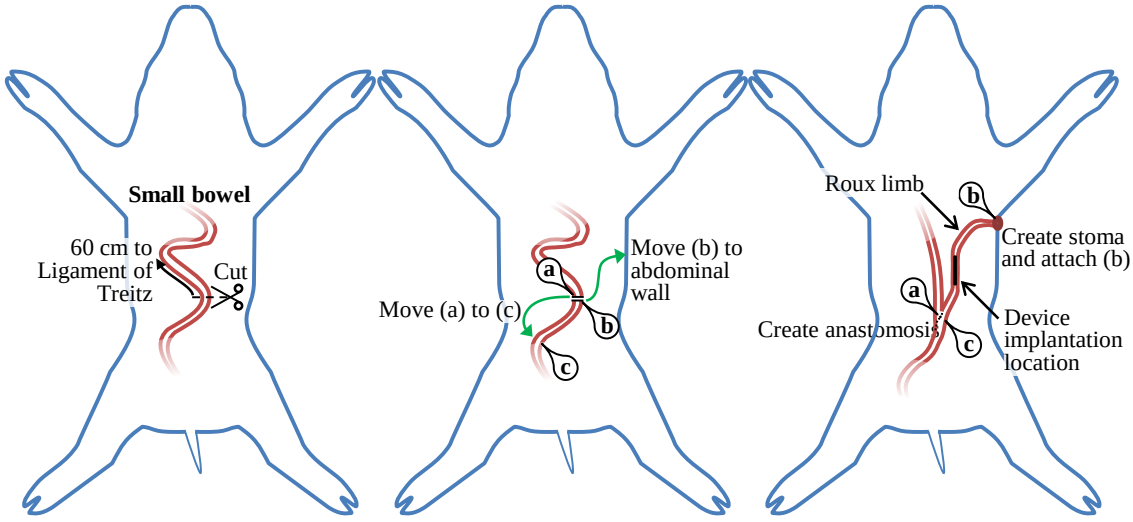


Figure 3.17. Surgical Implantation Schematic.
The Instrumented SMA Driven Ratchet was implanted in a Roux Limb created by cutting the small bowel and creating two open ends, (a) and (b), creating an anastomosis at (a) and (c), and connecting (b) to a stoma on the abdomen of the porcine model.

fascia of the abdomen, and the Roux limb was secured to the stoma at the fascia and skin. The final steps of the surgery were to route and secure the electrical wires from the Bowel Extender Circuit to the Pack Circuit through the stoma, complete the connection of the Bowel Extender Circuit with the Pack Circuit, and to secure the Pack Circuit to the center of the pig's back.

3.5.1.2. Expansion Approaches

The most effective approach to growing small bowel in a clinical setting is yet unknown, and a variety of approaches may be taken such as expanding the tissue at a constant rate, increasing the displacement rate with a non-linear or linear ramping profile, applying constant bowel tension, ramping tension, etc. The expansion approach used in prior studies of growing bowel tissue was constant rate impulsive displacement control, which may not be the most effective strategy in terms of the growth rate and/or resulting tissue health. Thus, enabling versatile studies of bowel growth in porcine models is a key feature of the Instrumented SMA Driven Ratchet. Three separate trials were completed with the following fundamentally different and potentially useful expansions approaches: constant rate impulsive displacement control, displacement rate limited load control, and constant load control. For the constant rate impulsive displacement control trial, the average daily displacement rate was constant, but the extension of the device was increased impulsively. In the displacement rate limited load control trial, the Instrumented SMA Driven Ratchet was manually commanded to actuate when the load dropped below 60 gf, but was also displacement rate limited to not step more than once per hour. The displacement rate constraint was included as a safety measure. In the constant load control experiment, the actuation threshold was lowered to 45 gf, but the displacement rate constraint was essentially removed. For each trial, a 36 hour no-expansion period following each implantation was observed to allow enough time for the porcine models to heal and recover.

3.5.1.3. Tissue Evaluation Plan

At the device removal and tissue harvest surgery, tissue samples are taken from the non-distracted Roux Limb as the control samples, from the distracted Roux limb, and from normal small bowel for comparison. During the distraction period, the Roux limb is not exposed to what the animal models ingest, except for cases of reflux into the Roux limb. The lack of nutrient rich contents flowing though the lumen of the Roux limb has an effect on its physiology, making the non-distracted Roux limb tissue sample the most appropriate control for evaluating the distracted

tissue segment. The analyses for evaluating the tissue health and function included evaluating the barrier function by measuring the tissue's transepithelial electrical resistance, evaluating growth by counting the percentage of proliferating cells stained by BrdU, and examining the general health by observing the tissue morphology from histologic slides.

3.5.2. *In Vivo* Results

Overall, the experiments were successful; the Instrumented SMA Driven Ratchet functioned well in the harsh *in vivo* environment, and a significant increase in the length of the bowel growth segment was achieved in each trial without negatively impacting its functionality or health.

3.5.2.1. Constant Rate Impulsive Displacement Control Trial

For the constant rate impulsive displacement control trial, the ratcheting mechanism was actuated at a constant daily rate of approximately 7 to 8 actuations (8.4 - 9.6 mm) with impulsive increases in displacement ranging from 3 to 4 actuations (3.6 - 4.8 mm) commanded twice daily. The load and displacement data are shown in Figure 3.17. The first expansion set of 3 actuations

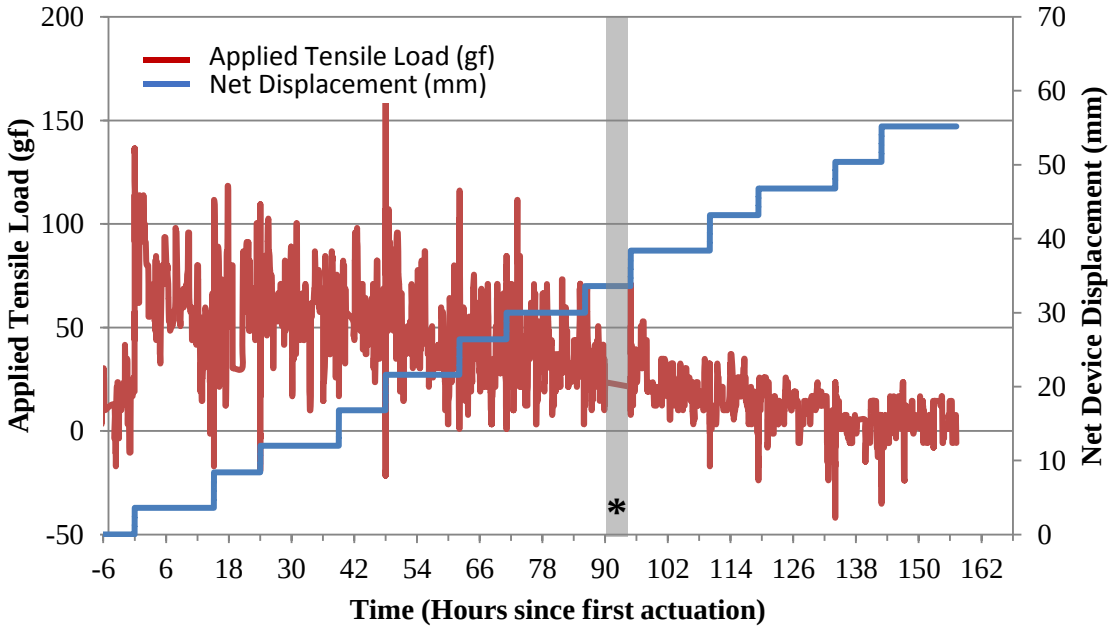


Figure 3.18. Load and Displacement Data Captured During Distraction Period of Displacement-Based Expansion Trial.

Despite the twice-daily expansion of the implanted device, the tensile load applied to the porcine small bowel continued to decrease during the distraction period. During the second half of the distraction period, the load fluctuated between 0 and 50 gf, suggesting that a greater rate of expansion could have been safety commanded, potentially resulting in a higher rate of tissue growth. *Region of communication loss due to removal of equipment from animal room.

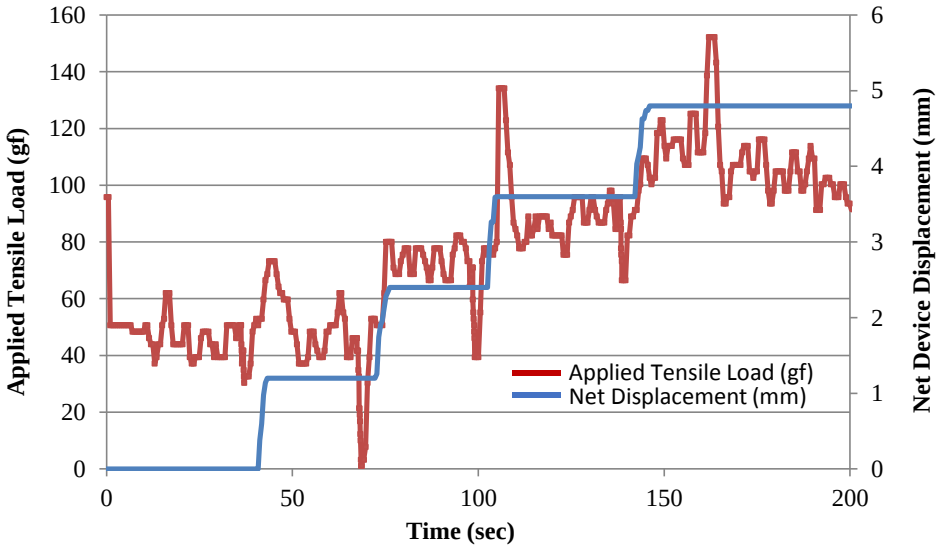


Figure 3.19. Effect of Actuation Close Up and the Measurement of Peristalsis.
By zooming into a subset of data acquired over the course of a couple of minutes, the effect of actuating the ratcheting mechanism can be seen. For each actuation, the applied tensile load increased by approximately 20 gf. These data also show effect of peristaltic action on the small bowel, which fluctuated the load at approximately 0.15 to 0.2 Hz.

was commanded 32 hours post operation. As a result of this expansion, the measured load increased dramatically from 23 gf to 135 gf. Although the safety limit of 90 gf on the applied load was exceeded by the final actuation of the three actuation set, the measured load reduced to 92 gf within the first minute after the expansion set and continued to decrease thereafter. After the first expansion set, the applied tension continued to decrease throughout the experiment despite the expansion of the ratcheting mechanism. While the rate used in this experiment was based off of the rate safely used in prior porcine studies with an un-instrumented bowel extender [2], these results suggested that a higher rate of expansion is possible, because as the load decreases the expansion rate can be increased while maintaining safe load levels.

The small intestine is a highly dynamic load environment due to peristaltic action, the involuntary periodic longitudinal and radial contraction of the smooth muscular layers of the small bowel. At the timescale of the entire duration of the experiment, peristaltic action, which is measured by the load sensor, looks like noise in the load measurement and obscures the increases in load due to expansions. To illustrate what is measured during a typical expansion set, Figure 3.18 shows a zoomed in portion of the experiment wherein a series of four actuations was taken. As shown in Figure 3.18, the tensile load following each actuation is increased as a result of the

Instrumented SMA Driven Ratchet straining the tissue. Also shown in Figure 3.18 is the measurement of approximately 0.15 to 0.2 Hz fluctuations in load due to peristalsis as captured by the load sensor. Capturing peristalsis successfully indicated that the load sampling frequency was appropriate, because peristalsis contributes the highest frequency content of the measured data. The measurement of peristaltic loads throughout the experiment was also an indicator of the small bowel health and motility.

3.5.2.2. Displacement Rate Limited Load Control Trial

To explore the potential for higher rates of growth, a load-based trial was conducted where the goal was to maintain a load of 60 gf on the bowel segment or higher. However, the rate of actuation was limited to one step (1.2 mm) per hour as a safety precaution, except for the initial impulsive displacement increase to raise the applied tension quickly. The load and displacement data for the distraction period of this trial are shown in Figure 3.19. For most of the distraction

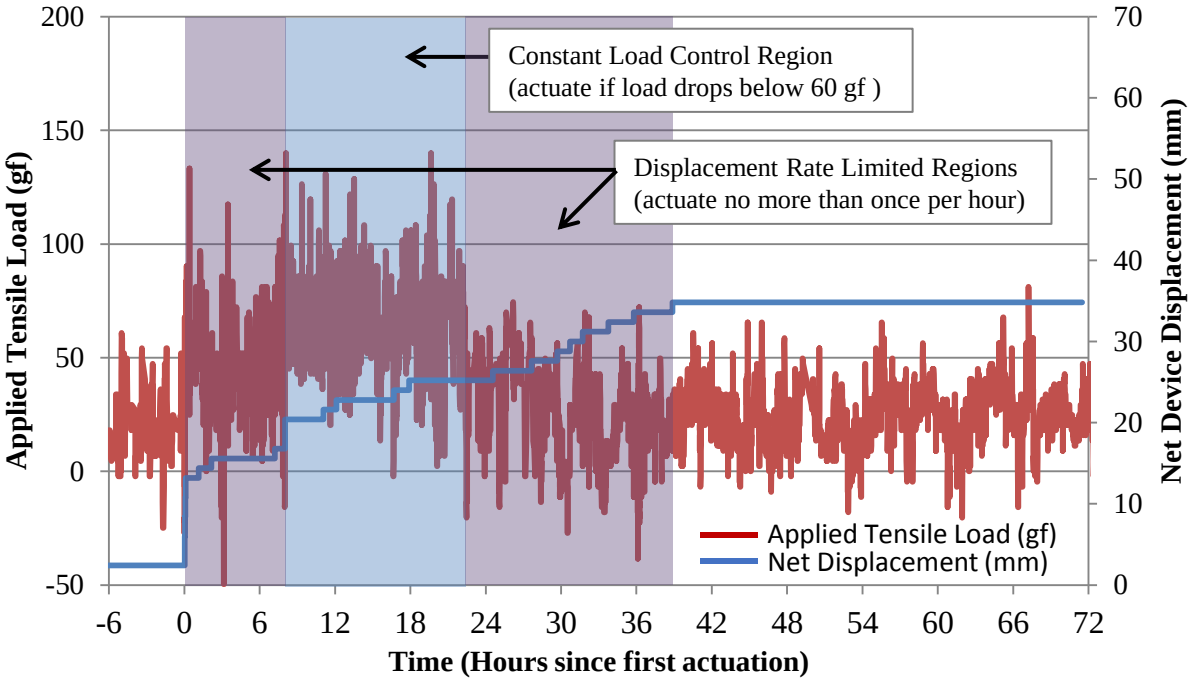


Figure 3.20. Load and Displacement Data Captured During Distraction Period of Displacement Rate Limited Load Control Trial.

During the Displacement Rate Limited Load Control Trial, the device was commanded to actuate if the measured bowel tension was below 60 gf. However, the device was also limited to actuate no more than once per hour regardless of the measured load. Thus, two regions of operation formed: the constant load control region, and the displacement rate limited region. Because the displacement rate limited region was action for 64% of the distraction period, these data suggest that a higher rate of safe bowel growth is achievable by relaxing the displacement rate constraint.

period, the load consistently dropped below 60 gf following an actuation, or remained below 60 gf, because the displacement rate limit was constraining the expansion. Thus, when the load was below 60gf, the expansion of the device was essentially displacement rate controlled. However, there was also a window, from approximately 8 to 22 hours, where the displacement rate limit was not constraining the device expansion. This window began at approximately 8 hours into the distraction period, when a second impulsive increase of the displacement was commanded to raise the load about 60 gf. For the following 14 hours, approximately, the displacement rate limit did not constrain the motion. Thus, in this window of the experiment, the expansion of the device was load-based. The resulting average daily extension rate was 2.1 cm per day. Compared to the constant rate impulsive displacement control trial, the total averaged extension rate for the displacement rate limited load control trial was approximately 2.3 times more rapid. However, because the displacement-rate constraint was active for most of the distraction period, the potential for an even higher rate of safe tissue growth was suggested.

3.5.2.3. Constant Load Control Trial

To further explore the potential for higher rates of growth, a constant load trial was conducted. For the constant load trial, the Instrumented SMA Driven Ratchet was set in an automatic load-based actuation mode, wherein the Instrumented SMA Driven Ratchet actuated when the average measured load dropped below 45 gf. The data for the constant load control trial are shown in Figure 3.20. The automatic expansion mode was enabled approximately 74 hours following the implantation. After enabling the automatic actuation mode, the Instrumented SMA Driven Ratchet actuated 23 times in the first 1.5 hours, bringing the applied bowel tension above 45 gf and extending the tissue by 27.6mm. During the 44 hour distraction period the Instrumented SMA Driven Ratchet expanded by 6.0 cm, giving an average rate of extension of 3.3 cm per day while maintaining a load on the bowel tissue in excess of 45 gf force. Compared to the constant rate impulsive displacement control trial, the constant load trial had an average extension rate approximately 3.5 times more rapid while maintaining safe magnitudes of applied small bowel tension.

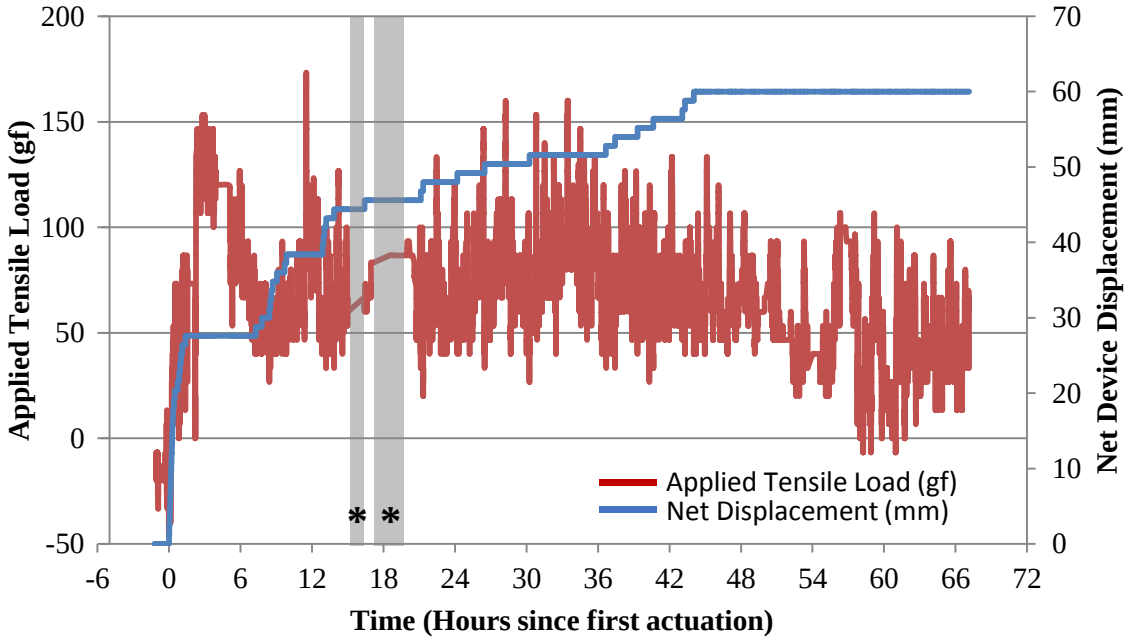


Figure 3.21. Load and Displacement Data Captured During Distraction Period of Load-Based Expansion Trial.

During the load based control trial in which the device was still extending, the applied tensile load was held between approximately 50 to 100 gf by the automatic actuation of the Instrumented SMA Driven Ratchet. The resulting rate of tissue expansion was 3.5 times faster than the constant rate impulsive displacement trial, suggesting that using the measured tensile load of the tissue to inform when to actuation can greatly and safely improve the tissue growth rate. *Regions of communication loss due to removal of equipment from animal room.

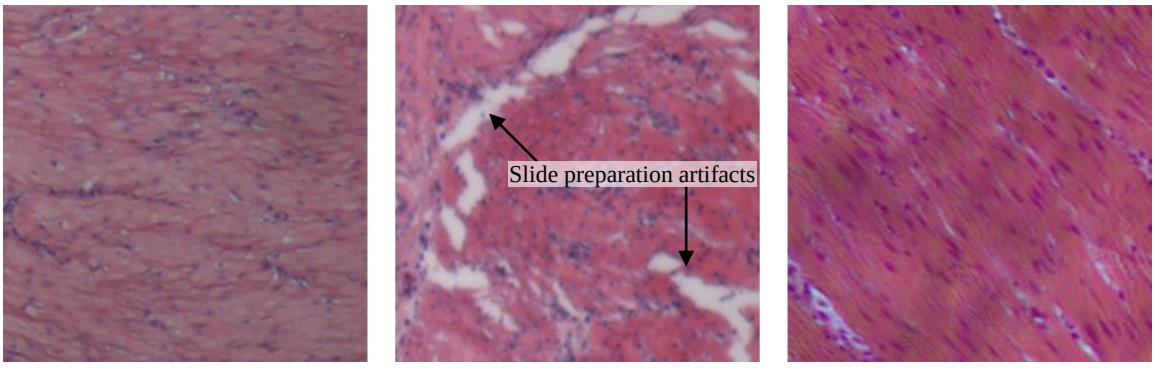
3.5.2.4. Medical Results

At the end of each of the trials, the net lengthening of the small bowel tissue was measured before and after detaching the Instrumented SMA Driven Ratchet from the tissue. Across all trials, the length of the small bowel tissue did not decrease after device removal. Thus, the net lengthening of the device equaled the amount of small bowel tissue grown. For the Constant Rate Impulsive Displacement Control Trial, Displacement Rate Limited Load Control Trial, and the Constant Load Control Trial, the net lengthening of the small bowel tissue was 5.5, 3.5, and 6.0 cm, respectively.

Tissue samples were taken during the explants of each trial to examine the health and functionality of the tissue. All grown tissue samples across trials did not show any gross evidence of damage such as tearing, necrosis, or ischemia. The health of the tissue samples were further evaluated through high powered microscopy for cell density and proliferation, as well as for signs

of microscopic damage such as tears, inflammation and edema. For all trials, samples from the distracted segments were compared to control samples taken from the Roux limb rather than normal bowel. This is because both the Roux limb control segments and the distracted segments were not exposed to enteral contents, potentially causing disuse atrophy, unlike the normal bowel segments which were exposed to enteral contents. Additionally, the normal bowel segments were not surgically manipulated during the implantation surgery, like the Roux limb and distraction segment.

Histologic slides of the distracted bowel segments from the three experiments were developed to look for signs of damage on a microscopic scale such as tearing, edema, inflammation, and general disruption of the tissue's structures. Across all trials, the only evidence of damage were the microscopic tears observed in the smooth circular muscle layer in the displacement rate limited load control experiment, shown in Figure 3.21b. However, it is not clear that the smooth muscle tearing is necessarily bad, because although different than smooth muscle, skeletal muscle requires tearing to promote growth and increase strength. Also, close inspection of the microscopic tears indicted that the tears were likely to be caused by slide preparation because of the absence of inflamed cell at the edges of the tears. Across trials, minor inflammation was observed in the distracted segments across trials, but the inflammation would be expected to decrease over time with the removal of the Instrumented SMA Driven Ratchet.

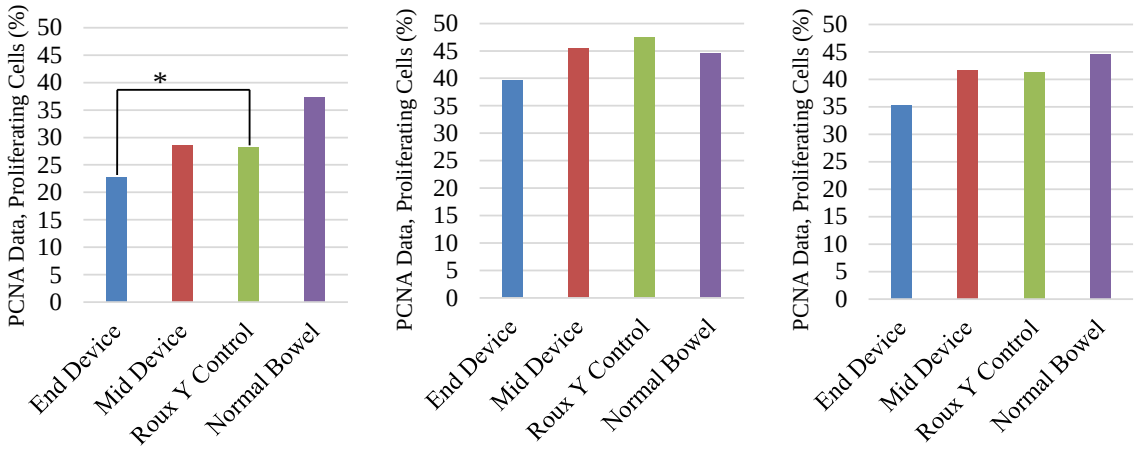


a). Constant Rate Impulsive Displacement Control Trial

b). Displacement Rate Limited Load Control Trial

c). Constant Load Trial

Figure 3.22. Circular Muscle Layer of Distracted Tissue Segments.
The only histological indication of tissue damage was seen in the circular muscle layer of the displacement rate limited load control trial. However, the tears seen in the figure were determined to be caused by slide preparation, because of the lack of inflamed cells seen at the edges of the tears. This result suggested that the tissue sampled during the explant was not mechanical damaged at a microscopic scale during the trials. Each square is approximately 350 by 350 μm.



a) Constant Rate Impulsive Displacement Control Trial

b). Displacement Rate Limited Load Control Trial

c). Constant Load Control Trial

Figure 3.23. Percentage of Cell Proliferation in Crypt/Villus Complexes of Distracted Tissue Segments.

Across all trials, the only statistically significant result was the difference between the Roux Y Control and End Device for the constant rate impulsive displacement trial. However, the medical significance of this result is minimal, as the overall maintenance of cell proliferation was observed across trials. Pairwise t-Tests were taken only for End Device against Roux Y Control, and Mid Device against the Roux Y Control. * indicates statistical significance ($p < 0.5$).

The percentage of proliferating cells within the crypt/villus complex of the distracted tissue segments is shown in Figure 3.22 for each trial. For this analysis, segments of distracted bowel tissue were collected from the middle of the distracted segments and at the ends of the distracted segments, the location of load application by the sutures affixing the tissue to the Instrumented SMA Driven Ratchet. Healthy small bowel has a high turnover rate of cells that form in the crypt/villus complex and subsequently slough off into the bowel lumen. For the samples collected, the only statistically significant difference in the percentage of proliferating cells between the Roux limb control and distracted segment was in the constant rate impulsive rate control trial (Fig 3.22, a) with the samples taken from the end of the distracted segment. However, the overall maintenance of the cell proliferation rates across trials was a positive indicator of the tissue health.

For the constant rate impulsive displacement control trial, the transepithelial electrical resistance (TER) of the tissue was measured to evaluate the barrier function of the tissue. The data are shown in Figure 3.23, and no statistical significance was found in the TER between samples. The maintenance of the barrier function is a positive indication of tissue health and functionality, because microscopic tears, holes, and tissue thinning would lead to decreased barrier function.

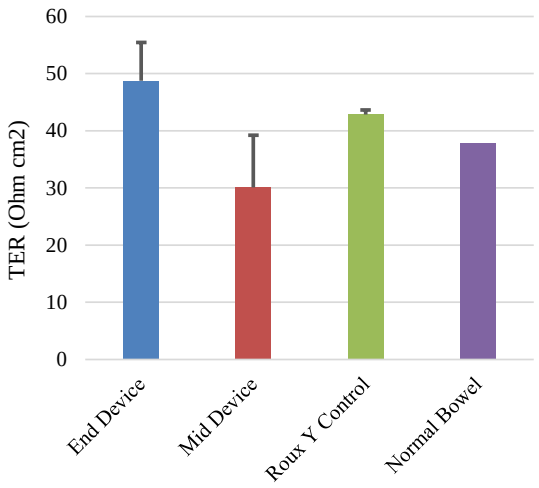


Figure 3.24. Transepithelial Electrical Resistance of Sample Bowel Tissue from Constant Rate Impulsive Displacement Control Trial.

The transepithelial electrical resistance of the grown tissue segment was not statistically significantly different from the Roux Y Control or the Normal Bowel. This result suggests that the grown bowel tissue was not perforated on a microscopic level and that the barrier function of the grown tissue segment was maintained.

Although not statistically significant, the increased TER of the samples from the middle and end of the distracted bowel segment suggests increased barrier function.

As a whole, the medical results across the trials have shown that there is little difference in the distracted bowel segments and their appropriate controls from the Roux Y Limb. The maintenance of cell proliferation, barrier function, and the morphology of the distracted samples indicates that the distracted small bowel tissue segments were actually grown, rather than simply stretched and/or permanently deformed.

3.6. Conclusion

To evaluate the best methods for exploiting the process of mechanotransduction in large clinically relevant animals, a fully implantable and instrumented bowel extending device was developed that is displacement controlled and instrumented to measure force and displacement. A novel graphical design methodology, the Reset View Design Methodology, was developed to design the device and can be used to design general SMA driven mechanisms reset by a spring or bias element. To predict the forces within the ratchet for the methodology, an analytical model of the kinematics and kinetics of the ratchet mechanism was developed which relied on the selection of tooth and pawl geometry based on packaging, stepping, and load-bearing constraints. To

determine the maximum safe bowel loads, a series of *ex vivo* and *in vivo* experiments were conducted. Using the Reset View Design Methodology, a prototype device was designed and used to experimentally validate the ratchet force model, which successfully predicted both the form of the internal forces and the peak magnitude that was used in the design methodology within 22%. The data acquisition and control system functionality was characterized and validated by calibrating the load and displacement sensors, observing the circuit to circuit communications with a logic analyzer, and measuring the range of the wireless communication system with the Instrumented SMA Driven Ratchet implanted in a porcine model. The device was successfully operated against static external loads up to 850 gf, far exceeding the minimum desired force output. The results of this research demonstrated the ability of the model-based design process to successfully produce a design capable of meeting and exceeding application specifications where the selection of the reset spring was greatly aided by the Reset View Design Methodology, which allowed the impact of the selected reset spring to be visually understood.

The Instrumented SMA Driven Ratchet was used to explore three different expansion approaches: constant rate impulsive displacement control, displacement rate limited load control, and constant load control. In the constant rate impulsive displacement control expansion, the average daily extension rate of the Instrumented SMA Driven Ratchet was set to a rate used safely in prior enterogenesis studies with porcine models [2,3]. The resulting applied tensile load on the tissue in the second half of the experiment did not exceed approximately 45 gf and continued to decrease despite the continued expansion of the device. This result suggested that greater rates of expansion than previously demonstrated were possible and prompted two further experiments utilizing the load sensor of the device to inform the expansion approach and increase the rate of tissue growth beyond what was previously possible. In the displacement rate limited load control trial, the Instrumented SMA Driven Ratchet was manually commanded to actuate when the load dropped below 60 gf, but a displacement rate constraint of one actuation (1.2mm) per hour was imposed for safety. Compared to the constant rate impulsive displacement control trial, the displacement rate limited load trial expanded the bowel tissue 2.3 times more rapidly. However, at the conclusion of the displacement rate limited constant load control experiment, the displacement rate constraint was active for 64% percent of the distraction period, during which the load fluctuated between 0 to 50 gf. Thus, an even greater possible safe rate of tissue distraction was suggested. In the constant load trial, the displacement rate limitation was eliminated and the

load threshold was reduced to 45 gf. Compared to the constant rate impulsive displacement control trial, the average daily expansion rate increased again, this time by approximately 3.5 times. These increases in the rate of tissue expansion were achieved at low magnitudes of load that did not approach safe limits. Furthermore, the across all trials, the health and functionality of the tissue was maintained when compared to controls.

The technology's ability to safely increase the rate of tissue growth has a large impact on the treatment approach for correcting SBS and the design of enterogenesis devices. In a clinical setting, if the planned implantation period of the enterogenesis device does not exceed 30 days, restrictions from the FDA lesson because the device is not considered a permanent implant (Investigational Device Exemptions, 21CFR812.3). More importantly, increasing the rate of small bowel growth will lead to lowered costs of care, reduced complication risks, reduced patient discomfort, and a more rapid transition from parenteral nutrition to a normal enteral diet.

These results have proven the reliability of the Instrumented SMA Driven Ratchet in the difficult *in vivo* environment and have shown the importance of enabling studies to explore different approaches to exploiting mechanotransductive small bowel growth by demonstrating that much greater rates of small bowel growth are possible. Further studies enabled by the Instrumented SMA Driven Ratchet will be important for informing the expansion rate of clinical devices for treating Short Bowel Syndrome. With the ability to provide reliable and repeatable displacement control, the measurement of net displacement and applied tensile load, the flexibility to change the expansion approach in real-time during implantations, and the system's full implantability, the Instrumented SMA Driven Ratchet represents a leap forward in device technologies for studying enterogenesis and the development of a clinical device.

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CHAPTER FOUR. EXPERIMENTAL STUDY OF SOFT TISSUE ATTACHMENT METHODS

Tissue-to-tissue and tissue-to-device attachment methods are of great importance to a broad range of surgical applications including tissue approximation, wound closure, anastomoses, joint repair and replacement, osteo-distraction, long-gap esophageal repair, the prevention of stent migration, and many more. With respect to the tension-induced correction of short bowel syndrome, the ability to reliably and safely transfer load from an extending mechanism to the bowel lumen is critical for success. While the mechanotransduction approach to treating SBS is promising, the safe transfer of load from the extending mechanism to the bowel lumen remains a challenge. In prior research studies on mechanotransductive enterogenesis, two primary attachment approaches have been used: end abutting attachments, and attaching through the lumen with sutures. Although these attachment methods were suitable for research, even though they were not reliable, there are significant disadvantages that limit their extension to clinical applications.

The end abutment approach for applying tensile small bowel load is the most common attachment approach previously used in studies of enterogenesis. Two embodiments of the approach have been used: double blind-ended, and single blind-ended with a stoma. In double blind-ended (sealed on both sides) end abutment, the segment of small bowel to be tensioned must be completely removed from the continuity of the gastrointestinal (GI) tract. The extending device is placed within the isolated segment, the ends of the isolated segment are sutured or stapled, and the continuity of the remaining GI tract is restored with an end-to-end anastomosis. As the implanted extending device expands, its ends abut the suture/staple lines, applying tension to the

isolated segment and inducing small bowel tension growth. The single blind-ended approach with a stoma is similar to the double blind-ended approach, but with the single blind-ended approach, only one end of the isolated bowel segment abuts the extending device. The other end of the isolated bowel segment is used to create a stoma through which an external extending device can apply bowel tension. Experiments with rats have used the single blind-ended with a stoma attachment approach to extend the ratio of isolated rat small bowel segments by a factor of 2 [1]–[3], and the double blind-ended approach was used to extend the small bowel tissue by factors ranging from 3.3 to 3.9 [4]–[6]. Additionally, experiments with pigs that used the double blind-ended approach have grown the isolated small bowel segment by a factor of 2 [7]. These research studies successfully applied the end abutment approach to small bowel attachment, as demonstrated by the significant lengthening of small bowel with both small and large animal models. However, important disadvantages greatly limit the clinical applicability of this approach. The greatest clinical disadvantage of the method is that it reduces the potential available length of small bowel, because after removing the device from the isolated tissue segment, any portion of bowel with sutures or staples must be discarded before the isolated tissue segment can be placed back into continuity with the GI tract. With each anastomosis required to isolate and restore the grown tissue segment, the discarded length of tissue accumulates and significantly reduces the gains in length made during the distraction period. Worse, the creation of bowel anastomoses requires invasive laparotomies, leading to the formation of adhesions which can lead to further bowel damage and resection when lysed during the surgery to place the grown small bowel back into continuity. To attach by end-abutment, at least three anastomoses must be created to isolate the tissue segment and then place the tissue segment back into the GI tract, leading to greater surgical cost, complexity, and an increased risk of enteral content leakage. Furthermore, by isolating the tissue segment during the distraction period, the tissue's contact with enteral contents is halted, potentially resulting in disuse atrophy.

The use of sutures to transmit force from the extending device to the small bowel wall was used in a prior study with rabbits [8], with the Curved Hydraulic Device, and with the Instrumented SMA Driven Ratchet. In the study with rabbits, the extending device was extraluminal and had two perforated semicircular tissue couplers that attached to the antimesenteric side of the small bowel with sutures. The extraluminal suture-based tissue couplers successfully transmitted force to the rabbit small bowel, inducing tissue growth and extending the tissue by a factor of 2.

However, the authors reported that the sutures cut through the bowel wall. Compared to the end abutment approach, sutured attachments have several advantages. Most importantly, the segment of small bowel tissue under tension does not need to be isolated from the continuous small bowel. Therefore, the need for several anastomoses and corresponding loss of small bowel length is eliminated. Additionally, suture-based attachments have the potential to enable the minimally invasive implantation of the extending device through the upper GI tract. However, suture based attachments require the small bowel to be perforated, the perforations create stress concentrations, and there is a significant risk of bowel tearing because load from the device is transferred to the tissue through the sutures. In the previous *in vivo* studies using the Curved Hydraulic Device (Chapter 2) and the Instrumented SMA Driven Ratchet (Chapter 3), one of the greatest challenges has been securing the devices to the bowel lumen with sutures. Essentially, the transfer of load to the small bowel through sutures elicits a process by which the sutures slip through the thickness of the tissue gradually. Interestingly, this has not led to bowel leakage, because the tissue heals during the process. Although successful experiments were completed with both the Curved Hydraulic Device and the Instrumented SMA Driven Ratchet, many experiments with both devices were not successful specifically because the devices became detached from the bowel wall. In the experiments where the attachments held, they did so barely – the sutures were close to slipping through the full thickness of the bowel wall. In an attempt to address this challenge with the Curved Hydraulic Device and the Instrumented SMA Driven Ratchet, pieces of Alloderm (denatured human skin) or Strattice (denatured pig skin) material were used to reinforce the area on the outside of the small bowel where the sutures were secured. This process has been moderately successful in lengthening the amount of time that tension can be applied through sutures, but it is not a permanent fix because the reinforcements also slip through the bowel wall. The challenge of transferring load with sutures is not limited to the application applying load to correct SBS. In patients with long-gap esophageal atresia, a condition where a large portion of the esophagus is absent, traction sutures are used in the Foker method [9] to apply tension on the esophagus and induce longitudinal growth. Similar to what was observed with the Curved Hydraulic Device and the Instrumented SMA Driven Ratchet, the traction sutures exhibit a tendency to cut or slip through the esophagus [10].

The mechanotransductive approach to correcting SBS has shown great promise in research studies where the attachments used were suitable in the research setting. However, to realize the

promise of the load-induced treatment approach in a clinical setting, there is a need for a tissue attachment approach that attaches more reliably and safely. The ideal attachment approach for this application would have the following characteristics:

1. Reliably transfer load from the extending device to the bowel wall without tissue slipping
2. Move freely through the bowel lumen without attaching during implantation, removal, and other purposeful repositioning
3. Allow enteral contents to flow through or around attachment (not cause obstruction), enabling the implantation of device in a continuous bowel segment
4. Not cause ischemia (reduction of blood flood) on attached tissue
5. Not cause or require microscopic or macroscopic tearing, perforation, and/or other mechanical damage to tissue
6. Enable minimally invasive surgical procedures. Minimize the surgical manipulation of remnant small bowel.

Unfortunately, the end abutment and suture-based attachment do not meet many of these criteria, limiting their clinical applicability.

This chapter presents an experimental design process to develop new approaches for small bowel tissue attachment and the identification of which attachment approaches have the greatest promise for meeting the above criteria with *ex vivo* and *in vivo* experiments. A broad range of conceptual attachment approaches are identified, and their fundamental architecture and operation are described. *Ex vivo* experiments with porcine small bowel are described for feasible conceptual approaches to characterize their ability to transfer load and slide through the bowel lumen freely for implantation/removal. Acute and long-term *in vivo* experiments are described for the attachments that performed well in the *ex vivo* experiments to evaluate the above six criteria, especially those concerning the safety of the attachment method (3, 4, and 5). Lastly, the wide range of attachment approaches are compared and a recommendation of the most promising attachment approach is made.

4.1. Attachment Approaches

As shown in Figure 4.1, seven main categorizations of approaches were identified: end-abutment, dilation, impingement, binding/kinking, adhesion, clamping, and tissue-piercing. Concepts that have not been evaluated in this study have the symbol of a circle crossed by a diagonal line, and each concept has been additionally categorized by location (intraluminal, transluminal, and extraluminal) with corresponding symbols.

Intraluminal attachment approaches are composed of components and features that are completely within the bowel lumen. Completely intraluminal attachment approaches are appealing because they have the potential to be implanted endoscopically through natural orifices and require little to no surgical manipulation of the bowel compared to transluminal attachment approaches. Compared to minimally invasive laparoscopic and open surgery, Natural Orifice Transluminal Endoscopic Surgery (NOTES) provides significant advantages such as reducing the risk for

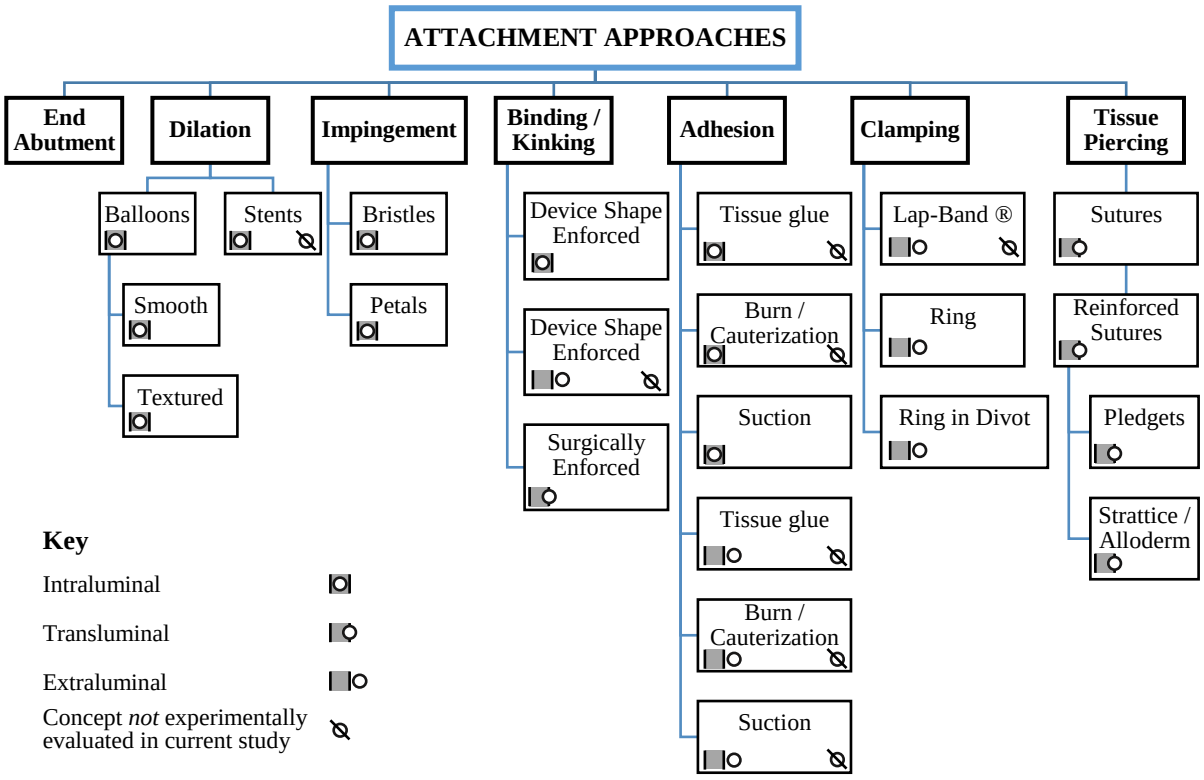


Figure 4.1. Small Bowel Attachment Approaches

Seven unique approaches to soft tissue attachment have been identified. Within each approach, the concepts are further categorized by whether the attachment is intraluminal, transluminal, or extraluminal. Most concepts were experimentally evaluated in this chapter. The symbol of a circle with a slash identifies the concepts that were not evaluated.

infection, because no device enters the peritoneal cavity, not requiring incisions, and reducing the recovery time. Additionally, using a NOTES approach to implanting the attachments will eliminate post-surgical adhesions, which make it difficult to isolate the applied tension on the bowel tissue segment. Despite these advantages, intraluminal attachments often rely on the application of pressure on the bowel lumen, such as end abutment, dilation, and impingement, and may thus lead to surgical complications such as ischemia and/or the creation of diverticula.

Transluminal attachment approaches are composed of components and features that interact through the thickness of the tissue or pierce it. Transluminal attachments that pierce the tissue, such as sutures, are able to apply high loads to small bowel tissue because the slipperiness of the tissue is not a factor. However, this approach requires bowel perforations that can lead to complications such as enteral content leakage, and does not enable NOTES device implantation. Additionally, extraluminal components are subject to greater design constraints (material choice, surface finish, etc) with respect to biocompatibility, because of their direct contact and potential interaction with tissues and organs within the peritoneal cavity. Transluminal attachments that do not pierce the tissue have intraluminal and extraluminal components that interact through the thickness of the tissue to achieve fixation. Like the intraluminal class of approaches, these approaches rely on applying pressure to the bowel lumen and may lead to ischemia and subsequent complications.

Extraluminal attachment approaches are composed of components and features that are complementally outside the bowel lumen and do not pierce the serosa. This class of attachment approaches does not enable NOTES device implantation, and like transluminal attachments, approaches is this class are subject to greater design constraints with respect to biocompatibility.

The branches of the concept tree (Figure 4.1) include end abutment, dilation, impingement, binding/kinking, adhesion, clamping, and tissue piercing. Each conceptual branch is defined and described below.

4.1.1. End Abutment

The most commonly used, simple, and successful approach to transferring load to the bowel in a research setting is end abutment. In this approach, a segment of small bowel is isolated from the GI tract and both ends of the segment are closed with a staple line or sutures. Within this isolated segment, the enterogenesis device expands, abuts the staple lines, and applies tension.

This attachment approach has been successfully used in enterogenesis studies with porcine models [7], [11], [12], and rat models [4]–[6]. In another surgical model, only one end of the isolated segment is closed with a staple line while the opposite end is fixed to a stoma, creating an ostomy. In this variant, one end of the enterogenesis device abuts the bowel tissue while the other is externally fixed relative to the skin of the animal model. This particular attachment approach was used successfully in enterogenesis studies with rats [1]–[3].

The end abutment approach has been a successful attachment method for conducting small bowel mechanotransductive tissue growth research, but the approach is limited in a clinical setting for several reasons. The main limitation of the end abutment approach is that it requires several anastomoses at the implant and explant surgeries. The requirement for anastomoses implies lengthier, more invasive surgical procedures, but more importantly, using multiple anastomoses significantly reduces the length of viable small bowel tissue. Additionally, the end abutment approach requires the growth segment to be isolated from the continuity of the GI tract, which can lead to disuse atrophy. These limitations have prompted the current study of alternative small bowel tissue attachments for use in a clinical setting.

4.1.2. Dilation

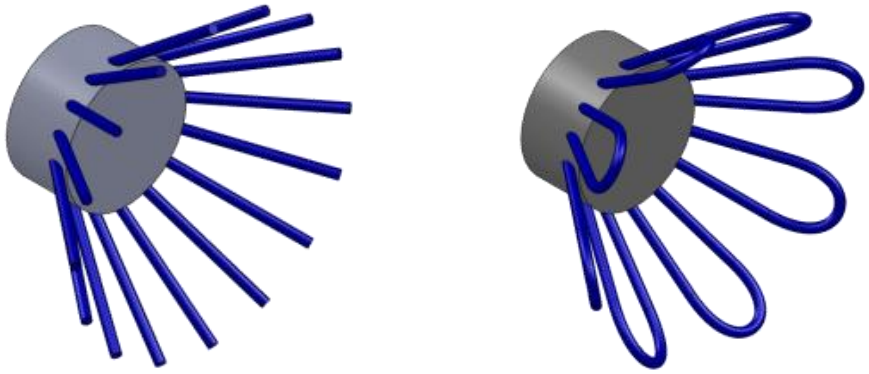
The dilation approach radially dilates the bowel to transfer longitudinal loads. Although not used in prior enterogenesis studies, this approach has been used in double-balloon endoscopy procedures to promote endoscope mobility and with stents that resist migration. In a double-balloon endoscopy procedure, an endoscope equipped with two balloons transverses the bowel in a ratcheting fashion, where the balloons alternate between gripping (inflated) and releasing (deflated) the bowel. This approach to endoscopy has allowed surgeons much greater access to previously difficult to reach sections of the small intestine, improving the management and treatment of GI bleeding, chronic diarrhea, abdominal pain, and other intestinal pathologies. Stents are used to reestablish or improve the patency of obstructed small bowel and esophageal segments, and treat GI perforations and fistula. However, the migration of stents is a potentially life-threating complication. To prevent stent migration, the stents must radially grip the lumen of the tissue in which it was deployed. Both esophageal and intestinal stents are often designed with wider diameter ends and features like barbs and petals to further prevent migration.

Although balloons and stents are currently clinically used within the small intestine, neither has been used specifically to apply longitudinal small bowel tension. However, because of the prohibitive cost of medical stents, only balloons were evaluated *in vivo* to determine their ability to transfer load and address potential surgical complications.

4.1.3. Impingement

The impingement approach aims to grip the bowel tissue by using features that impinge and/or partially pierce the bowel lumen with minimal radial tissue dilation. Two impingement approaches were developed in this study: bristles and petals. The bristles and petals, shown in Figure 4.2, are designed of a compliant material such that the application of increasing load causes the bristles/petals to bend away from each other, increasing the effective diameter of the attachment. The compliance of the bristles and petals can be designed such that at near injurious applied loads, they bend all the way backward – allowing the tissue to slip and reducing the tension.

Prior to the current study, this approach to soft tissue attachment has not been evaluated in studies with living biological tissue, and there were safety concerns related to both the bristle and petal concepts. For bristles, the main safety concern is that they tear and or pierce through the full thickness of the bowel wall because they have pointed tips, causing enteral content leakage,



Bristle Concept **Petal Concept**

Figure 4.2. Bristle and Petal Based Impingement Approaches

The bristle and petal based attachments were designed to provide direction dependent attachment performance. In the direction in which the bristles or petals are pointed, the attachment force should be greater because the bristles or petals bend backward and increase the effective diameter of the attachment as the attachment is displaced relative to the bowel lumen. As the attachment moves in the opposite direction, the attachment force is decreased because the bristles and petals do not impinge the bowel lumen.

inflammation, sepsis, and possibly piercing other loops of small bowel and or other tissues within the peritoneum. For petals, there is also a safety concern that they will pierce through the bowel wall, but by a different mechanism. The main concern is that the petals will cause localized ischemia in the tissue that contacts the rounded ends of the petals, leading to tissue necrosis, weakening, and eventually perforation. Embodiments of these two attachment approaches were fabricated and evaluated in a series of *ex vivo* experiments, to evaluate their ability to transfer force, and in acute *in vivo* experiments, to evaluate the safety risks of using these attachments.

4.1.4. Binding / Kinking

The binding/kinking approach is to route the tissue around one or more sharp (small radius) bends. This approach can be implemented intraluminally or extraluminally by attachments that guide the tissue around sharp bends, and this approach can also be implemented surgically, by creating looped portions of small bowel with sutures. This approach was developed based on the observation that sharp bends and kinks in small or large bowel tissue often impede the motion of surgical instruments like endoscopes.

Like the impingement approach, this approach to soft tissue attachment has not been evaluated in prior studies with living biological tissue. To address concerns related to the functionality and safety of this approach, an *in-vivo* experiment was completed with the surgically enforced embodiment of this approach.

4.1.5. Adhesion

The adhesion approach to gripping is to bond or adhere to either the innermost layers, the mucosa and submucosa, or outermost layer, the serosa, of the small bowel. Several approaches in this class of attachments include suction, the use of a “tissue” bonding glue, and by burning/cauterizing the bowel such that it sticks to the heating element. Although both concepts are included here for completeness, a tissue glue appropriate for this application was not identified in this study and the burning/cauterizing approach was considered unreasonably dangerous. Furthermore, although tissue glue could potentially attach to the epithelium, the turnover rate of epithelial cells is on the order of 2 days. Thus, the effectiveness of attaching with tissue glue is potentially limited to just a few days. To evaluate the functionality and safety of the suction approach, an acute *in vivo* study was performed.

4.1.6. Clamping

The clamping approach uses an external clamp which narrows the bowel lumen or presses the bowel lumen onto an intraluminal component of the attachment. A currently practiced procedure using a Lap-Band®, which is essentially an adjustable diameter clamp, is a treatment alternate to sleeve gastrectomy and gastric bypass. The Lap-Band® was designed to reduce the diameter of the esophagus above the stomach rather than to attach or grip the tissue. Thus, two embodiments of the clamping approach were evaluated in *in vivo* experiments to address concerns related to the attachment performance and safety of this approach.

4.1.7. Tissue Piercing

The tissue piercing approach uses transluminal components, like sutures, to secure intraluminal or extraluminal components to the bowel wall. This approach is currently used clinically in the Foker [9] method to treat Long-Gap Esophageal Atresia (LGEA). The Foker method induces esophageal growth by the application of force through traction sutures. However, one common complication of this approach is that the sutures cut through the thickness of the esophagus.

In the earliest reported study of tension-induced small bowel growth [8], in which healthy rabbit models were used, the extending mechanism of the device attached to the tissue with extraluminal semicircular tissue couplers that were sutured to the bowel. The study reported complications related to the sutures cutting through the rabbit small bowel, which was also a common complication in this dissertation, even when the sutures were reinforced with pledgets, strips of Alloderm, or strips of Strattice. To better understand this phenomenon, many *in vivo* experiments were completed with both the SMA Ratcheting Device and the Curved Hydraulic Device.

4.2. Experimental Evaluation of Attachments

To evaluate the attachment approaches, a series of *ex vivo*, acute *in vivo* (short term, on the order in minutes), and longer term *in vivo* experiments (up to and exceeding one week) were conducted. The goal of the *ex vivo* and acute *in vivo* experiments was to determine if the attachment approaches satisfied the following requirements:

1. enable the application of high tensile force without slipping,

2. facilitate surgical implantation and removal by sliding easily though the tissue lumen,
3. not cause acute tissue ischemia, and
4. not cause tissue injury such as perforation and/or tears.

Attachments that could not meet these requirements were not evaluated further in longer term *in vivo* experiments. The goal of the longer term *in vivo* experiments was to determine if the remaining attachment approaches could meet the aforementioned requirements in addition to the following:

1. not block the flow of enteral contents,
2. enable high net growth,
3. cause tissue ischemia,
4. cause tissue injury such as perforation and/or tears, and
5. attach reliably for implantation periods exceeding one week.

The following sections describe the range of experiments applied to evaluate these criteria for each attachment approach.

4.2.1. *Ex Vivo* and Acute *In Vivo* Experiments

Acute *in vivo* experiments were conducted on a range of the attachment concepts to determine how well they attach/detach and if they pose the risk of health complications like ischemia and bowel perforations and/or tears. Because *ex vivo* experiments cannot be used to determine the risk of ischemia, most attachments were evaluated in acute (less than 1-2 hour) *in vivo* experiments. The following approaches were not evaluated in either *ex vivo* or acute *in vivo* experiments: end abutment, binding/kinking, clamping, and tissue piercing. From prior research using the end abutment approach, it capabilities, advantages, and disadvantages are well understood. Therefore, the end abutment approach was not further examined in this study. Similarly, the acute behavior of sutures for attaching to bowel is understood, but how the small bowel tissue reacts to the sutures placed under tension over the course of weeks is not. Because of this, the examination of sutures centers on *in vivo* experiments lasting one to two weeks. The binding/kinking and the clamping approach were evaluated in only longer term *in vivo* tests because the interaction of the extending device and the tissue were similar to the end abutment approach. These similarities were enough to consider the concept safe and to not require prior *ex vivo* or acute *in vivo* testing. The attachment

approaches presented here include the dilation approach (smooth and textured balloons), the adhesion approach (suction), and the impingement approach (bristles and petals).

4.2.1.1. Dilation Approach – Smooth and Textured Balloons

A range of balloons, with and without texture, were evaluated in acute *in vivo* experiments to determine their ability to apply traction on the small bowel without slipping and without causing ischemia. The dilation approach to intraluminal attachment has been used in double balloon endoscopy procedures, where two balloons are inflated and deflated to attach and release the tissue in a ratcheting fashion to maneuver the endoscope along the bowel. The success of balloons for attachment in double balloon endoscopy supported their further study with the goal of measuring their gripping force and evaluating their risk of causing ischemia.

4.2.1.1.1. Dilation Prototypes

Many concepts were fabricated based on the various permutations of balloon type, the presence of a texturing material, and the type of texturing material. The balloons were taken from endotracheal (ET) tubes (Kimberly-Clark: Microcuff, 7mm ID tube, and Sheridan/HVT 9mm ID tube), and Foley urinary catheters (Bard Medical: BARDEX 5cc Balloon, 30FR catheter). In some trials, the balloons were textured by the application of loose mesh bagging material (Figure 4.3c) or abrasive material taken from scrubbing sponges (Figures 4.3d and 4.3e). Of these prototypes, several were eliminated early in the experiments. For example, the Foley urinary catheters did not inflate symmetrically about the axis of the catheter (Figure 4.3g), like the ET tubes (Figures 4.3a and 4.3b). Additionally, the loose mesh bagging material (Figure 4.3c) did not make any significant impact on the gripping performance of the balloon attachments. Because of this, only the ET tube balloons were evaluated with (Figures 4.3d and 4.3e) and without (Figures 4.3a and 4.3b) the abrasive material from scrubbing sponges as a texturing agent.

4.2.1.1.2. Dilation Approach Experimental Procedure

To evaluate the dilation approach, the initially deflated balloons were inserted into the small bowel lumen of live porcine models, inflated to a measured pressure from 0 to 60 mmHg, and then manually pulled on with a tension measuring probe with increasing tension until the balloon

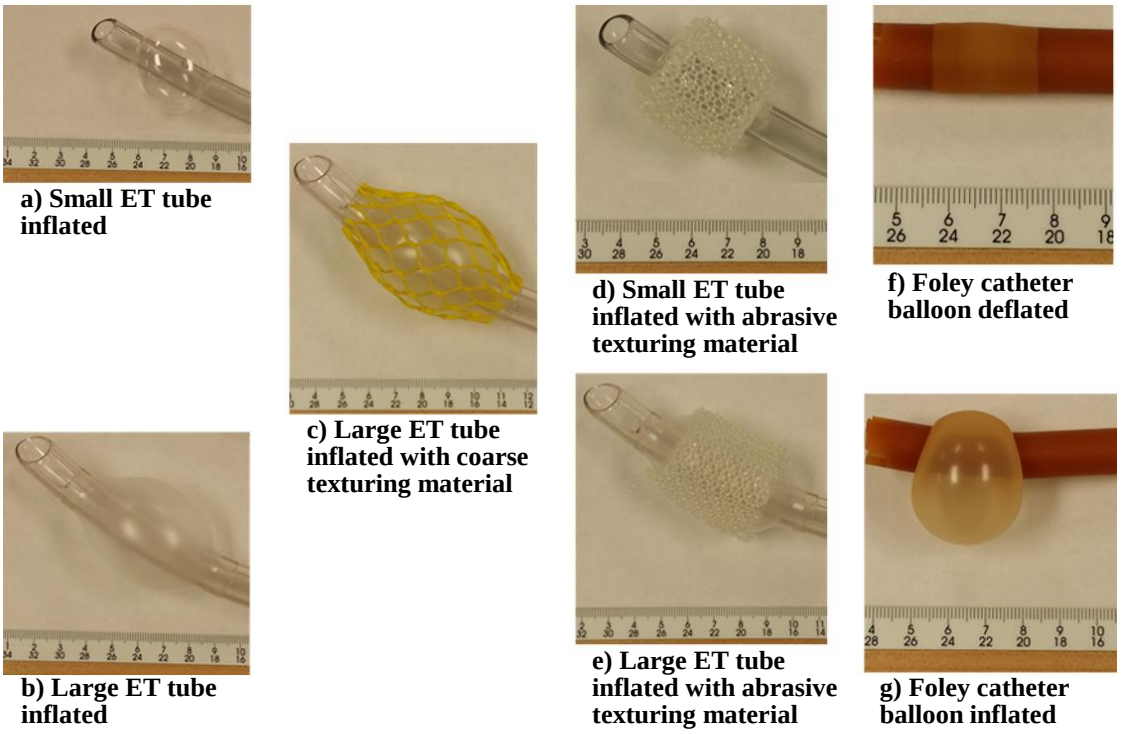


Figure 4.3. Dilation Prototypes.
Several embodiments of the dilation approach were fabricated from endotracheal tubes (a and b) and Foley catheters (f and g). The use of texturing materials was also explored with the endotracheal tubes (c, d, and e).

slipped. The condition of the balloon slipping was evaluated visually during each trial, using the vasculature of the small bowel as reference points, and was defined as any longitudinal motion of the attachment relative to the bowel wall. The health of the small bowel tissue was grossly determined by visually checking the tissue for any signs of macroscopic mechanical disruption and acute ischemia, which was indicated by tissue blanching.

4.2.1.1.3. Dilation Approach Results

Results from these experiments are plotted in Figure 4.4. Four different prototypes were evaluated: a large ET tube balloon with and without texture, and a small ET tube with and without texture. The basic trends of this experiment were intuitive: the application of greater pressure, the greater size of the balloon, and the presence of the gripping material all increased the slipping force of the attachments. Interestingly, the abrasive scrubbing material made a very large impact on the performance of the attachments without significantly scraping the delicate mucosal layer of the bowel segments. This result was determined by the lack of mucosal scrapings embedded in the material when its balloon was removed from the bowel segment. Furthermore, because the addition

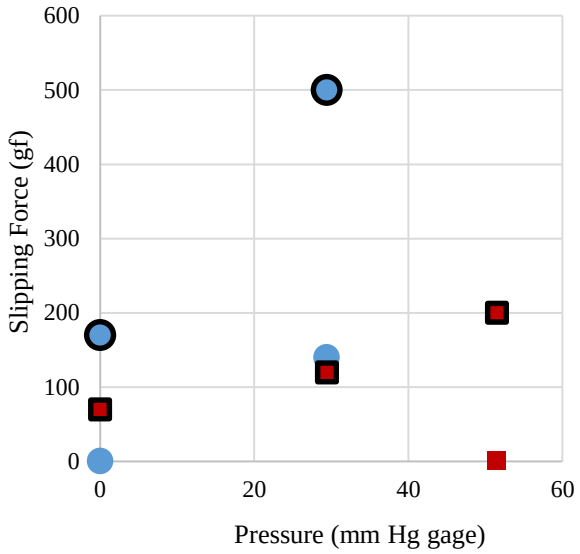


Figure 4.4. Slipping Force of Dilation-Based Attachments.

The slipping force as a function of balloon pressure of several dilation-based attachments was measured with *in vivo* porcine small bowel tissue. The slipping force recorded corresponds to the measured force at which the onset of attachment movement relative to the bowel was observed. The square data represent the small ET tubes and the circle data represent the large ET tubes. The outlined data are the balloons modified to have texture, while the data without the outlines are smooth. The data show that increasing pressure increases the slipping force, and the addition of texture greatly increases the slipping force, even for balloons that were not inflated.

of the scrubbing material greatly reduced the need for the balloons to apply high pressure in order to attach, the pressure applied to the small bowel and therefore the risk of acute ischemia was significantly reduced. Unfortunately however, the application of the scrubbing material also made both balloon sizes have a significant gripping load even when the balloons were completely deflated. In fact, the large balloon could not be inserted without using a plastic sheath between the material and the bowel wall. This is a disadvantage because these attachments would be difficult to surgically implant and remove because they do not slide though the tissue.

4.2.1.2. Adhesion Approach – Suction

The potential of suction as an attachment approach was evaluated in an acute *in vivo* test with a single prototype. This concept required an experiment with living tissue because there was a concern that creating suction on the bowel wall would cause ischemia.

4.2.1.2.1. Suction Prototype

The prototype (shown in Figure 4.5) was constructed from two 10 cc syringes (0.63 inch outer diameter) connected by silicone tubing, with the suction syringe modified by having its plunger

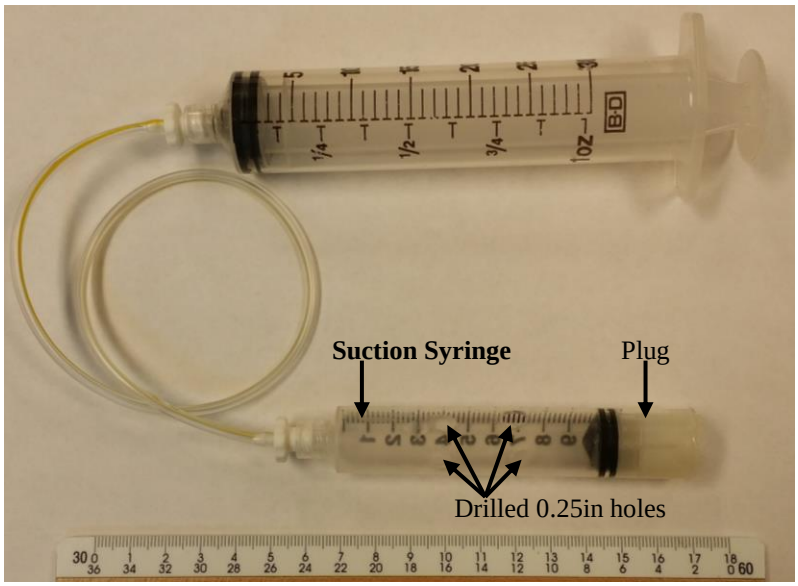


Figure 4.5. Prototype of Suction Attachment.

The suction attachment prototype was made by drilling four holes into a standard 10 cc medical grade syringe and fixing the syringe seal relative to the syringe body to create a plug. The suction syringe was then connected to a 30 cc syringe with silicone tubing. When tissue prevents the flow of air through the holes of the suction syringe, vacuum pressure can be made within the suction syringe by pulling the plunger of the 30 cc syringe, holding the tissue to the attachment.

affixed to the syringe housing and the addition of 4 evenly spaced 0.25 inch diameter holes that were staggered lengthwise by approximately 0.5 inches.

4.2.1.2.2. Suction Approach Experimental Procedure

To evaluate this embodiment of the suction approach, the suction syringe was intraluminally placed in a segment of living porcine small bowel, and three levels of vacuum were applied with the unmodified syringe and a pressure sensor: 0, approximately 50, and approximately 70 mm Hg of vacuum pressure. For each vacuum pressure level, the corresponding longitudinal force required for the suction-syringe to slip was measured.

4.2.1.2.3. Suction Approach Results

The results of this experiment are shown in Figure 4.6, which shows that increasing the vacuum pressure increases the slipping force of the attachment. Compared to all other attachment approaches, this embodiment of the suction approach had the capability to switch from a very low insertion and removal force to a very high gripping force. This is advantageous, because a low insertion and removal force would greatly facilitate the surgically implantation and removal of the attachment and potentially enable minimally invasive surgical techniques to be used. However,

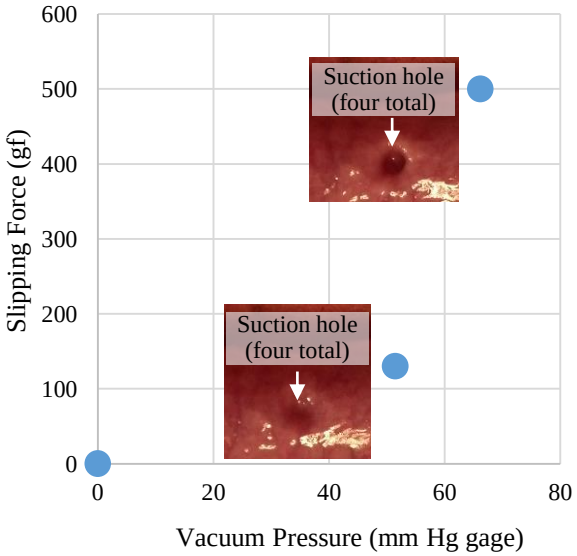


Figure 4.6. Slipping Force of Suction Approach.

The suction approach results show that when desired, the attachment force can be made as low as zero and as high as 500 gf acutely. The longer term effectiveness of the approach was not evaluated however, because the apparent risk of tissue ischemia at the hole locations indicated by the tissue blanching.

there are concerns about how this approach would perform in a longer-term experiment, because the suction holes are likely to become clogged with enteral contents. To completely overcome the clogging issue, each suction hole would need to have its own pneumatic line, allowing each suction hole to be flushed independently. Additionally, there were concerns that the suction approach would lead to bowel ischemia because there was significant tissue blanching observed where the tissue overlapped the holes. Therefore, this approach was not further considered for longer term *in vivo* experimentation.

4.2.1.3. Impingement Approach – Bristles and Petals

A range of bristle and petal based concepts were created with superelastic nickel-titanium wire segments of varying lengths, diameters, circular densities, and angles. The choice of bristle material was made because nickel-titanium is biocompatible and because of its superelasticity, it can significantly bend to aid in its surgical insertion and removal without plastically deforming the attachment. The bristle and petal prototypes were evaluated in *ex vivo* segments of porcine small bowel tissue as well as in acute *in vivo* experiments. The goal of the *ex vivo* experiments was to

measure the gripping performance of the attachments, while that of the *in vivo* experiments was to evaluate the risk of mechanical damage and ischemia on the bowel.

4.2.1.3.1. Impingement Approach *Ex Vivo* Experimental Procedure

For the *ex vivo* experiments, a custom experimental setup was created with the capability to simultaneously measure the displacement of the attachment and the force applied by the attachment to the tissue segment. The *ex vivo* experiments were conducted with porcine small bowel segments that were originally stored at below freezing and then thawed in a warm saline bath. The bowel segments were further prepared by rinsing out their contents and removing the mesentery with surgical snips.

The experimental procedure was to first mount the attachment within the bowel lumen on a monofilament line pulled through a set of pulleys by a displacement-controlled stepper motor. A tissue tension measuring force sensor was mounted in series with the monofilament line to measure the magnitude of force transmitted from the attachment prototype to the bowel lumen. The free ends of the *ex vivo* bowel tissue sample were then secured relative to the housing of the custom experimental setup with sutures. The final step was to use the stepper motor to pull on the attachment prototype while recording the attachment displacement and tissue force. The return of the attachment to its original location was achieved by a near constant load spring affixed to the attachment opposite the monofilament line. Based on an experimental characterization of the spring's constitutive behavior, the spring's contribution to the load measurement was removed in the post-processing of the collected data.

4.2.1.3.2. Impingement Approach *Ex Vivo* Experimental Results

The characteristic behavior of these attachments is shown in Figure 4.7, which plots the force transmitted to the bowel segment by the attachment against the displacement of the attachment relative to ground, not relative to the tissue. The blue data (upper curve) were taken as the attachment displacement increased, showing that the bristle attachment was able to apply increasing loads until leveling between 350 and 425 gf. Minimal attachment slipping, if any, was observed prior to the plateau region. In the plateau region, the attachment alternated between gripping the tissue and slipping, which is indicated by the rise and fall of the applied load. The slipping of the bristle attachment occurred when the applied bowel tension was enough to buckle the attachment bristles backward, stopping the bristle points from impinging in the tissue. The red

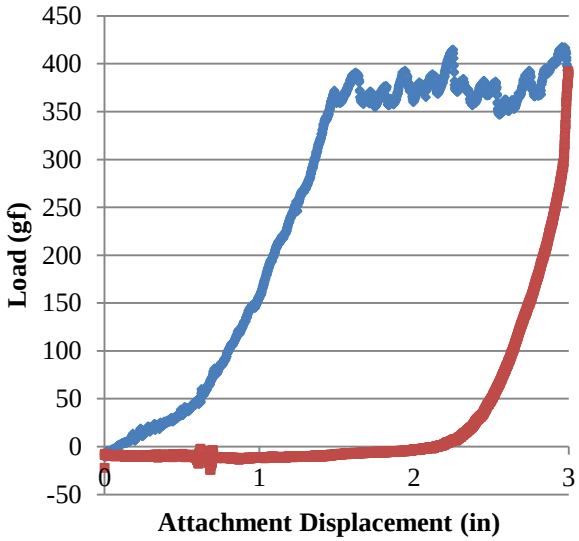


Figure 4.7. *Ex Vivo* Gripping Performance of the Bristle Approach.
The characteristic *ex vivo* load-displacement performance of the bristle approach is shown. As the bristle-based attachment was pulled through the bowel lumen (upper curve), it attached to tissue without slipping as the tensile load on the tissue increased to above 350 gf. At this stage, the bristles began to buckle backward (due to the force of the bowel lumen) and then snap back into place, causing the attachment to alternately slip and grip as the force fluctuated between 350 and 425 gf until the attachment displacement was 3 inches (relative to ground). As the attachment displacement was decreased from 3 inches back to zero (lower curve), the attachment stopped slipping relative to the bowel lumen and the applied bowel tensile rapidly decreased to zero. These data were typical for both the bristle and petal based attachments, however the bristle based attachments were able to apply greater tensile load before plateauing than the petal based attachments.

data (lower curve) were taken as the attachment displacement decreased, which shows the applied bowel tension rapidly dropping to zero force. The hysteretic behavior resulted predominately because the attachment slipped several inches along the tissue lengthwise as the attachment displacement was increased. Although the data shown in Figure 4.7 are for an embodiment of the bristle concept, the characteristic behavior illustrated by the plot was the same for other bristle and petal embodiments. However, the bristle attachments were able to apply higher loads than the petal attachments.

4.2.1.3.3. Impingement Approach Acute *In Vivo* Experimental Procedure

The risk of mechanical tissue damage and ischemia were evaluated for the bristle and petal attachments in segments of live porcine bowel tissue. The experiments were conducted by intraluminally placing the attachments and visually observing for tissue perforation, macroscopic tearing, mucosal layer scrapping, and ischemia.

4.2.1.3.4. Impingement Approach Acute *In Vivo* Experimental Results

Typical results from several experiments are illustrated by Figure 4.8, which shows the state of the tissue after the intraluminal placement a bristle attachment (Figure 4.8a), a petal attachment (Figure 4.8b), a petal attachment modified to be a sharper by bending the petals (Figure 4.8c), and a petal attachment modified to reduce the risk of ischemia by lining the petals with silicone (Figure 4.8d). Although they can reliably apply high load to the small bowel, the complication of the bristle approach perforating the tissue is almost certain to occur within days of implanting such an attachment for a longer-term experiment. The risk of puncture is increased not just because the bristles are thin and sharp, but because they create a highly localized area of weakened ischemic tissue at their tip. This risk is serious because if the bristles perforate the bowel lumen, it will cause enteral content leakage that can lead to severe infection, sepsis, and potentially death. Additionally, bristles that have perforated the bowel lumen may also puncture adjacent segments of small bowel and other organs. Although to a lesser extent, the petal and sharp petal attachments also caused localized areas of tissue ischemia where they contacted the bowel lumen, which can be seen as the white areas where blood was not properly perfusing the tissue. Therefore, for implantation periods

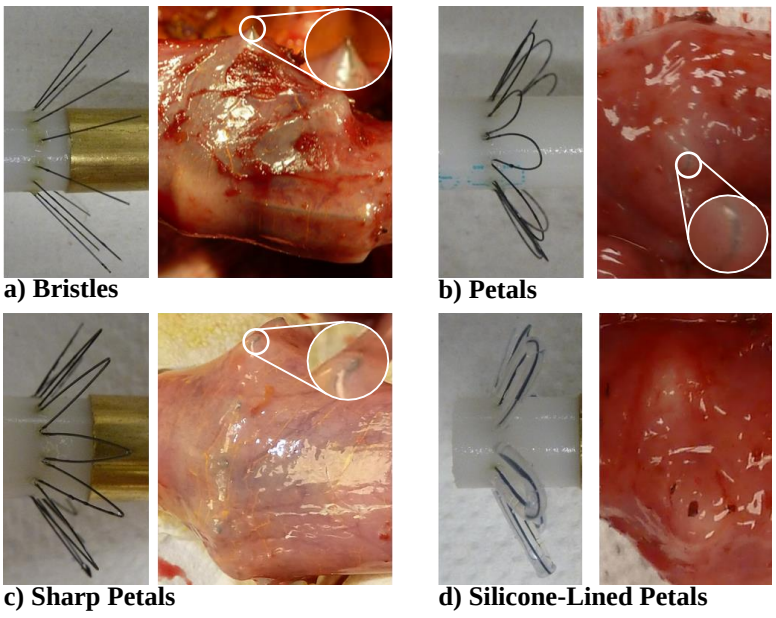
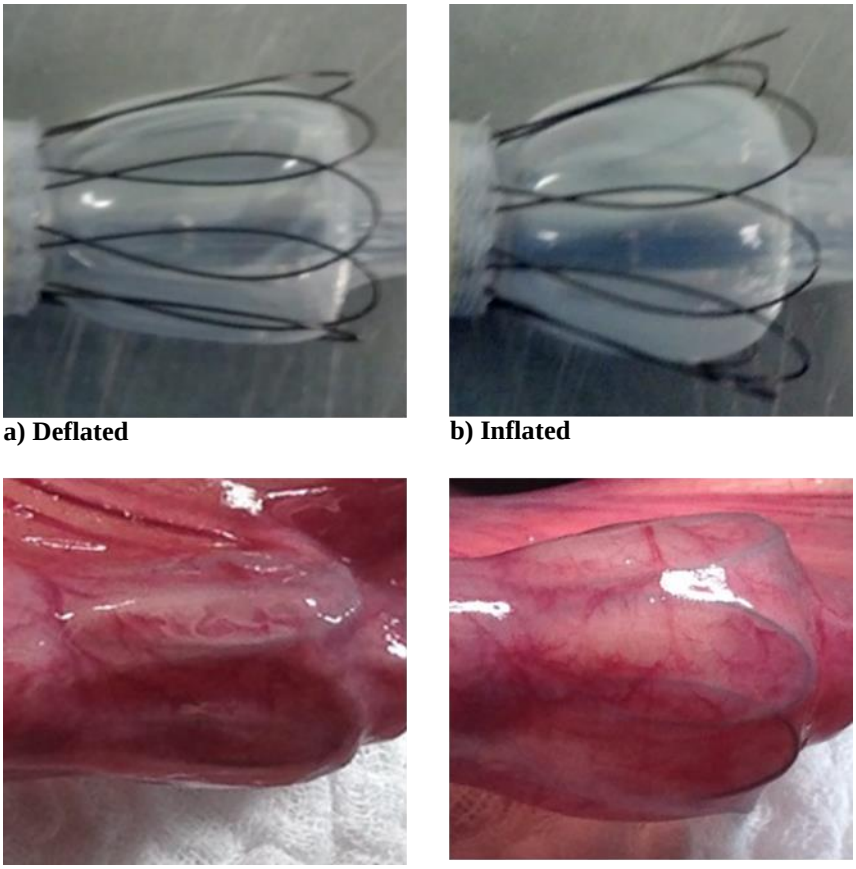


Figure 4.8. Bristle and Petal Based Attachment Implanted in Live Porcine Tissue.
The bristles and petals were evaluated with *in vivo* porcine small bowel tissue to evaluate their risk of bowel ischemia and perforation. The attachments that most effectively attached to the bowel lumen, the bristles, petals, and sharp petals, were also the most likely to caused bowel perforation. While the silicone-lined petals did not present the risk of bowel perforation secondary to ischemia, the attachment easily slid through the bowel lumen without gripping.

greater than approximately one week, the risk of tissue ischemia leading to necrosis and subsequent bowel perforation is high. Lining the petals with thin silicone tubing greatly reduced the risk of ischemia and the subsequent cascading complications. However, the lined petals slipped along the bowel lumen readily, applying less than 50 gf.

For the bristle and petal approaches, the acute *in vivo* experiments revealed an important tradeoff between the gripping performance and the risk of bowel perforation and/or ischemia. The approaches seemingly rely on the application of areas of localized pressure to create points of fixation along the bowel wall. The more localized the area of pressure is, the greater the risk of ischemia and the better gripping performance there is. To overcome this tradeoff, active petal-based attachments that are pneumatically actuated with balloons were developed (Figure 4.9). In



a) Deflated **b) Inflated**

c) Deflated, Implanted **d) Inflated, Implanted**

Figure 4.9. Balloon-Actuated Petal Approach.

To enable the petal-based attachment to operate in engaged and disengaged attachment modes, the concept of spreading the petals with a balloon was explored with *in vivo* segments of porcine small bowel. In addition to being able to disengage from the small bowel lumen for implantation, removal, and purposeful repositioning, the disengaged mode better allowed blood to perfuse the bowel tissue surrounding the attachment. However, even with the balloon deflated, the tissue drapes around the ends of the petals, prohibiting the attachment from sliding freely along the bowel lumen.

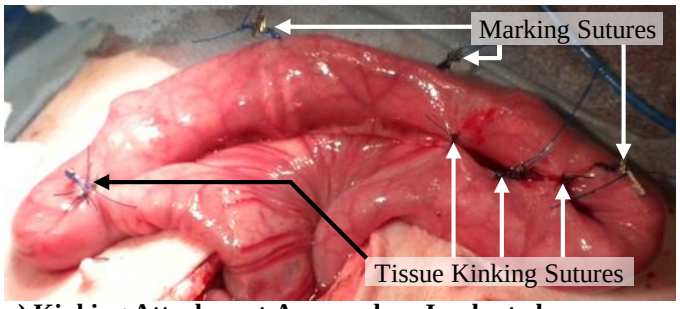
an acute *in vivo* experiment, the balloon-actuated petals provided high tensile loads similar to passive petal-based attachments while the balloon was inflated. With the balloon was deflated, the gripping force was significantly reduced, but so was the risk of ischemia. Figures 4.9c and 4.9d show that when the balloon is inflated, areas of blanched (whitened) tissue appear along the petals and on the face of the balloon, whereas the tissue surrounding the deflated attachment is well-perfused by blood. The balloon-actuated petal concept can be used to safely apply tensile bowel load intermittently, where the duration of time that the load is applied would be set to reduce the risk of ischemia. Following periods of applied bowel tension, the attachments would be deflated to allow blood to reperfuse the tissue. Unfortunately, the attachments did not slide easily along the bowel lumen in the deflated state, due to the manner with which the bowel tissue draped around the petals. This cycle of load application and tissue reperfusion could be repeated to safety apply intermittent bowel tension.

4.2.2. One to Two Week *In Vivo* Experiments

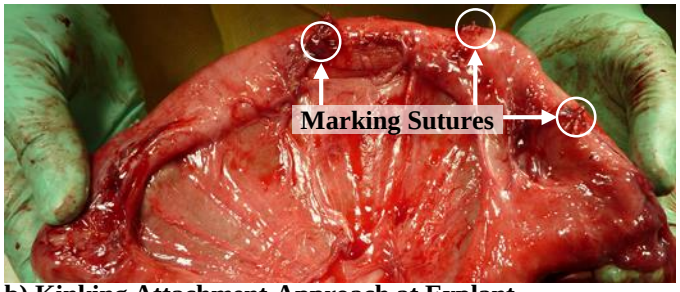
Longer *in vivo* experiments were conducted to evaluate the attachment performance and potential surgical complications associated with a series of attachment approaches that demonstrated promise in the *ex vivo* and/or acute *in vivo* experiments. These approaches included the binding/kinking approach, the clamping approach, the tissue piercing approach, and the dilation approach with textured balloons. The challenge of attaching safely and reliably for longer implantations was much greater than that for acute experiments, because over time, the small bowel adapted and dramatically remodeled itself in the presence of the attachments. To apply loads with attachments in these longer term experiments, extending devices were required to drive the motion of the tissue attachments. The extending devices included the Curved Hydraulic Device, the Instrumented SMA Driven Ratchet, and a reciprocating single-stage linear hydraulic device with a 3.4 cm stroke.

4.2.2.1. Binding / Kinking Approach – Surgically Enforced

During routine colonoscopies, the colonoscope can often become stuck within the large intestine due to sharp bends along the tissue. Although problematic during a colonoscopy, this phenomenon was evaluated as a beneficial attachment approach for small bowel in a live porcine animal model. To evaluate if bends in the small bowel could be used as attachments in a fashion similar to end-abutment, an experiment was conducted by placing the Curved Hydraulic Device



a) Kinking Attachment Approach as Implanted



b) Kinking Attachment Approach at Explant

Figure 4.10. Surgically Enforced Tissue Kinking Approach.

Tight bends in the small bowel tissue on both sides of the Curved Hydraulic Device were enforced by sutures as a means of evaluating the tissue kinking approach. In addition, marking sutures were placed along the length of the small bowel to determine the amount of tissue growth at the explant. At the explant. At explant, the measured tissue growth was only 0.5 cm, despite the 9.5 cm expansion of the Curved Hydraulic Device.

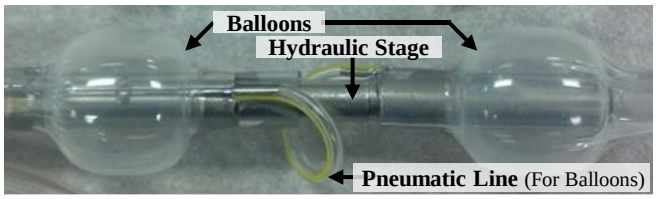
into a Roux limb of small bowel and then surgically enforcing sharp bends around the device using sutures, as shown in Figure 4.10. In addition to the sutures used to enforce a sharp bend on both ends of the Curved Hydraulic Device, marking sutures were also placed to track the growth of the tissue. During a two-week implantation period, the Curved Hydraulic Device was extended by approximately 9.5 cm. However, at the explant, the measurement from the marking sutures indicated that the tissue lengthened by only approximately 0.5 cm. Therefore, it was not an effective attachment approach for the application of tension-induced small bowel tissue lengthening and it is not recommended for similar applications.

4.2.2.2. Clamping Approach – Extraluminal Ring

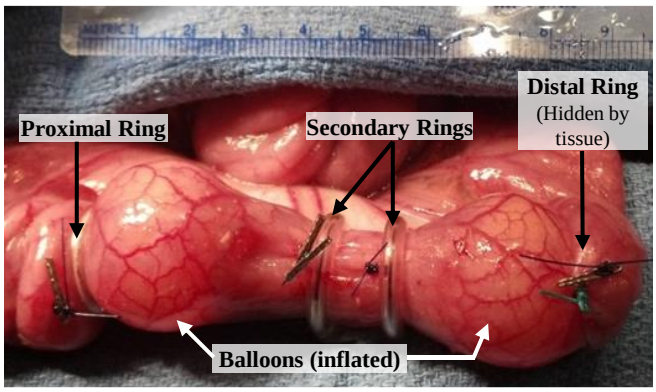
The use of extraluminal rings was explored in two *in vivo* experiments to evaluate their potential, using two different extension devices: a reciprocating single-stage linear hydraulic device, and the Curved Hydraulic Device. The reciprocating single-stage linear hydraulic device is shown prior to implant (Figure 4.11a), at implant (Figure 4.11b), and at the conclusion of a one-week long implantation period (Figure 4.11c). For this approach, the intended operation was that

the inflated intraluminal balloons would push on the extraluminal rings, which were placed though surgically created mesenteric defects. The intended points of fixation were the areas of tissue with heightened pressure due to the interaction of the balloons (when inflated) with the rings.

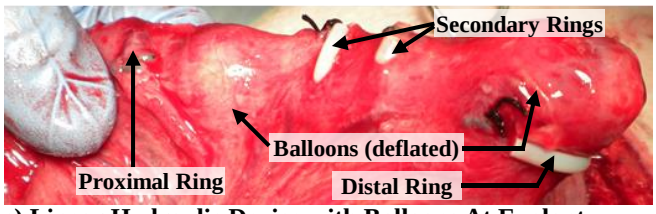
To evaluate the intraluminal balloon with an extraluminal ring attachment approach, the linear hydraulic device was placed through the stoma of a Roux limb of porcine small bowel with its balloons deflated. After device placement, an external syringe was used to inflate both balloons through a shared pneumatic line. The proximal and distal rings were then placed through surgically created mesenteric defects, which are small holes in the mesentery, such that there was minimal slack in the tissue between the attachments. Secondary rings were also placed to provide attachment points of fixation. Additionally, marking sutures were placed along the tissue to create



a) Linear Hydraulic Extending Device with Balloons



b) Linear Hydraulic Device with Balloons At Implant



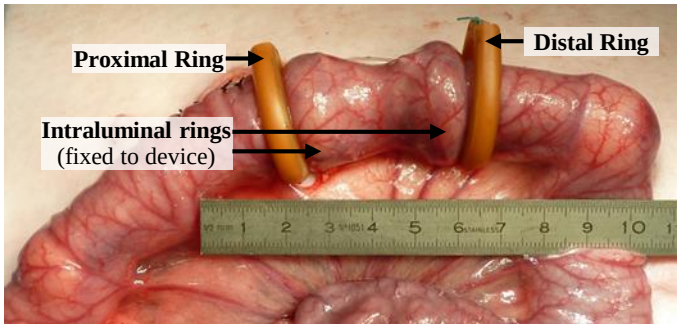
c) Linear Hydraulic Device with Balloons At Explant

Figure 4.11. Clamping Approach with Single Stage Linear Hydraulic. Using a single-stage hydraulic device as the extension mechanism, an embodiment of the clamping approach using internal balloons and external rings was evaluated *in vivo* in an experiment lasting one week. At explant, the tissue segment length was increased by 10-15% out of a possible 40% (limited by device stroke).

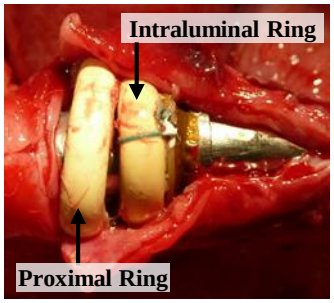
reference points for measuring the change in tissue length. Ideally, after growing the length of bowel between the outermost rings, the balloons could be deflated, repositioned, and reinflated (under fluoroscopy) such that the distal balloon engages one of the secondary rings, allowing for greater tissue growth. However, the main goal of this experiment was to grow the tissue between the attachment rings by 3.4 cm, the maximum stroke of the linear hydraulic device, for an increase in the tissue length of 40%.

During the implantation period, an attempt to reposition the distal balloon attachment under fluoroscopy was not successful because the separation of the proximal and secondary rings was not sufficient to fit the collapsed device. At the explant surgery (Figure 4.11c), the marking sutures placed during the implant surgery were located and they indicated that the tissue grew by approximately 10% to 15% out of a potential 40%. Thus, the attachments were able to transfer enough tension such that the small bowel grew, but more than half of the potential tissue growth did not occur due to attachment slipping. Clinically, this extent of slipping is not acceptable because the amount of small bowel growth is already greatly limited by the space within the peritoneal cavity, especially for neonates, and this amount of slipping essentially reduces the potential tissue growth further by than a factor of more than 2. At the attachment sites, the health of tissue was maintained during the implantation as was demonstrated by a lack of inflammation, tissue necrosis, tears, or perforations. The extraluminal rings, which were made of silicone tubes, were not embedded in the tissue and were easy to remove. Although there was concern that the rings could cause tears in the mesentery because they were placed through mesenteric defects, this complication was also not observed.

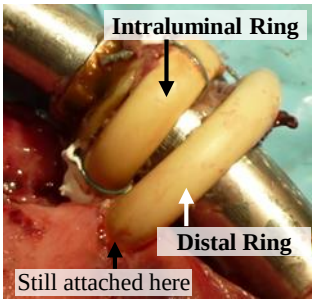
The complete lack of observed surgical complications and the increase of tissue length, albeit small, prompted a further study of this attachment approach using the Curved Hydraulic Device, which is capable of much greater net expansion (15 cm) but does not reciprocate. The idea of the attachment is the same as with the linear hydraulic device, but instead of using balloons to push on the extraluminal rings, intraluminal rings were used. All of the rings were made from cut segments of 18 Fr latex tubing. The surgical implantation procedure and the use of marking sutures to track tissue growth was identical with the experiment using the linear hydraulic device. The goal of this experiment was to double a length of bowel tissue from approximately 4.5 cm to 9 cm over the course of 2 weeks. Several radiographs were taken during the implantation period to



a) Curved Hydraulic Device with Rings At Implant



b) Proximal Ring at Explant



c) Distal Ring at Explant

Figure 4.12. Curved Hydraulic Device with Ring Attachments.

Using the Curved Hydraulic Device as the extension mechanism, the clamping approach was further evaluated using internal rings (mounted on the device) and extraluminal rings made of latex 18 Fr Foley catheters. After the one-week experiment, the originally extraluminal rings were located within the bowel lumen, leaving the device mostly detached. The distal end of the device was barely attached on a small part of the extraluminal ring at the explant.

validate that the actual expansion of the Curved Hydraulic Device was matching the expected expansion, which it did successfully.

At the explant surgery of this experiment, the expansion of the Curved Hydraulic Device was more than sufficient to achieve the tissue growth goal. However, the initially extraluminal rings were found within the lumen of the small bowel, as shown by Figures 4.12b and 4.12c. The proximal extraluminal ring (Figure 4.12b) was completely detached from the mesentery and bowel tissue, while the distal extraluminal ring (Figure 4.12c) was barely attached to the bowel at one site. The envelopment of the extraluminal rings into the bowel lumen was not expected, and did not occur during the experiment using the linear hydraulic device. This is perhaps because the experiment with the linear hydraulic device lasted for one week instead of two weeks. In the process of the extraluminal rings becoming intraluminal rings, there were no health related surgical complications such as enteral content leakage or bowel tears, as evidenced by the lack of an inflammatory response within the peritoneal cavity seen at the explant. The growth of the segment

could not be measured at the explant, because the marking sutures placed during the implantation could not be found. Although the tissue probably did grow a little prior to the complete detachment of the proximal ring, this approach did not demonstrate reliable attachment performance and is not recommended for this or similar surgical applications.

4.2.2.3. Tissue Piercing Approach – Sutures and Reinforced Sutures

The use of sutured attachments was a focus of this study because sutures are used extensively by surgeons and they are able to transfer high loads to tissue acutely. To evaluate their potential for transferring load from a bowel lengthening device to the bowel wall, experiments (n = 12) were conducted with bare sutures (n = 2) and sutures reinforced by pledgets (n = 2), Alloderm (denatured human dermis, n = 2), and Strattice (denatured porcine dermis, n = 6). The experiments used both the Instrumented SMA Driven Ratchet and the Curved Hydraulic Device as the bowel lengthening device in experiments with implantation periods ranging from 1 to 4 weeks, distraction periods ranging from 2 to 27 days, and targeted amounts of small bowel longitudinal tissue growth of 50% and greater.

The condition of the sutured attachments were photographed at the end of each experiment, and a determination of whether the attachments held or slipped was made. If the attachments held, the sutures were still visible on the outside of the bowel wall and the bowel tisse was not separable

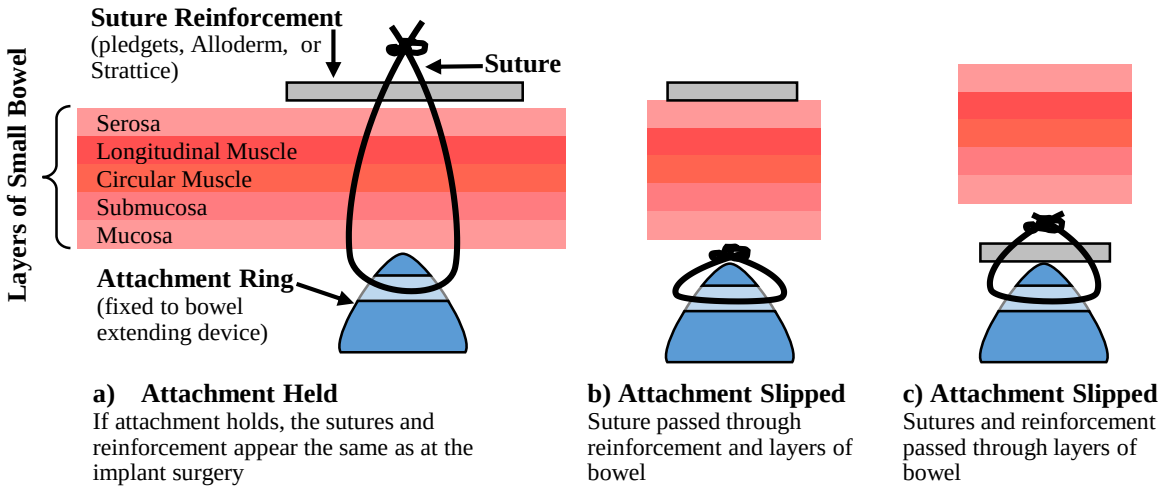


Figure 4.13. Schematic of Suture Attachment Outcomes.

Three outcomes of using the sutures with and without reinforcement were observed at explant. If the attachments held, the sutures were still visible on the outside of the bowel at explant. The attachments slipped through the tissue leaving the reinforcing material on the outside of the bowel (b), and in some experiments, both the reinforcing material and sutures slipped through the tissue (c).

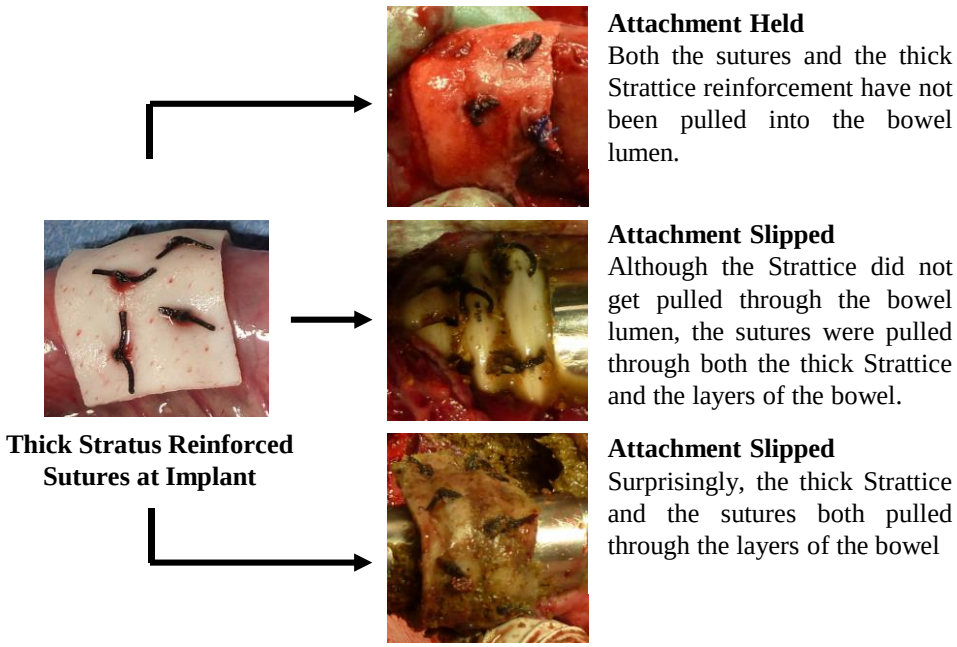


Figure 4.14. Outcomes of the Sutured Attachment Approach.

Photographs of the reinforced sutures show the transformation of the attachment during the distraction period. Even when the attachments held, the reinforcing material is in the process of integrating into the bowel and slipping. In experiments where the attachments slipped, the reinforcing material was left on the outside of the bowel lumen in some experiments. In some experiments, both the sutures and the reinforcing material slipped through the full thickness of the bowel wall.

from the device without cutting the sutures. The reinforced suture attachments slipped in two ways, as shown by Figure 4.13. When the sutured attachments slipped, it was either because just the sutures pulled through the reinforcing material and the layers of small bowel (Figure 4.13b), or the sutures *and* the reinforcing material pulled through the bowel (Figure 4.13c). The lack of observed peritonitis in the experiments where the attachments slipped (n = 5) strongly suggests that when the sutures slip through the bowel, it does not lead to bowel perforation and subsequent enteral content leakage. Furthermore, these results suggest that the event of the sutures slipping is not abrupt, because it takes place on a timescale that allows the tissue to heal around the sutures. When the attachments did hold, as shown by Figure 4.14, the reinforcing component, whether it was pledgets, Alloderm, or Strattice, was observed to be in the process of slipping through the bowel wall. The slow and safe detachment of this class of attachments may be potentially advantageous clinically, because it facilitates the removal of the bowel lengthening device by minimally invasive surgery. However, it is difficult to determine how long the attachments will hold and they are unlikely to perform reliably from patient-to-patient.

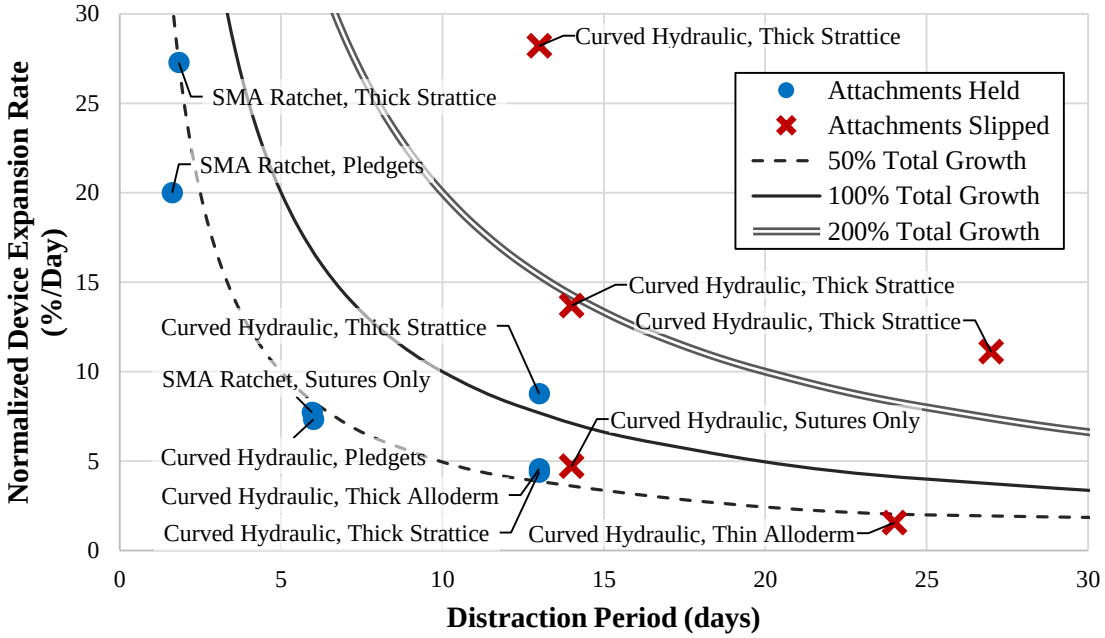


Figure 4.15. Tissue Piercing Approach Results – Normalized Expansion Vs. Distraction Period. The attachment holding and slipping results for bare sutures, and sutures reinforced with thin Alloderm (denatured human skin), thick Alloderm, and thick Strattice (denatured pig skin) are shown as a function of the distraction period and the normalized device expansion rate (device expansion rate divided by the initial attachment-to-attachment length). These results show that the sutures, even when reinforced, did not stay attached for experiments exceeding two weeks. No dependence on the normalized device expansion rate was suggested by these data.

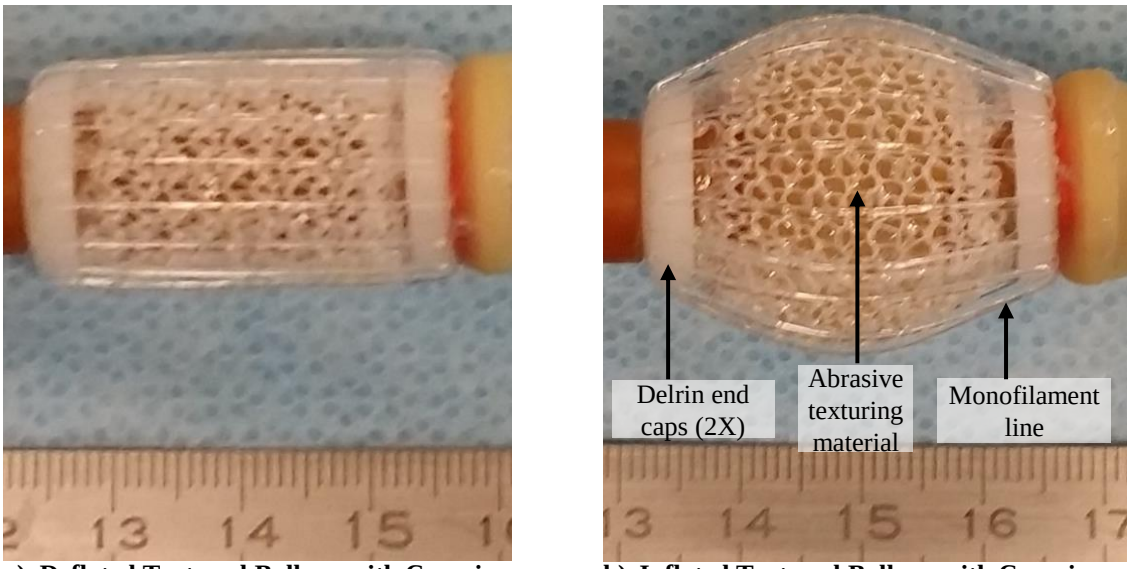
Several key factors have been identified in the success of the suture-based attachment approach: length of distraction period, normalized rate of attachment separation (device expansion), and the magnitude of the applied force on the tissue from the sutures. The magnitude of the applied force was measured in only the experiments using the SMA Ratcheting Device (n = 3), because the Curved Hydraulic Device does not have force instrumentation. As a result, the data were analyzed based on the rate of normalized attachment separation and the length of the distraction period, which is defined by the window of time during which the bowel tissue was actively strained. Figure 4.15 shows the relationship between these two factors and the success of the attachment, where the blue data indicate success and the red data indicate experiments where the attachment slipped. The data suggest that high rates of normalized device expansion may be achieved if the distraction period is less than approximately 2 to 3 days, and that even very low rates of normalized device expansion (less than 0.025 %/day) are not feasible for distraction period exceeding 2 weeks. In fact, the suture-based attachments did not hold in any of the experiments in which the distraction period exceeded two weeks. Additionally, the grouping of data near (13 days,

0.05 %/day) suggested that reinforcing the sutures with either Alloderm or Stratus improves the reliability of the attachment compared to just using sutures.

4.2.2.4. Dilation Approach – Dilating Fenestrated Mesh

In the acute *in vivo* experiment with textured balloons, the approach was very promising with respect to their ability to grip the bowel lumen when inflated. When inflated and attached, the tissue with which the balloons made contact remained well perfused with blood. Thus, the risk of ischemia with the approach is minimized. Unfortunately however, the abrasive material used to texture the balloons made the attachments grip well even when the balloons were deflated. This is an important disadvantage because an extending device using these attachments would be difficult and potential unsafe to implant, reposition, and remove. Thus, a method to cover the balloons/texture when deflated and uncover the balloons/texture when inflated was developed to improve the detachment ability of the attachment without reducing its attachment ability.

The attachment prototypes, shown in Figure 4.16, were modified by the addition of elastic cords suspended over the texture of balloon by machined Delrin end caps. The Delrin end caps



a) Deflated Textured Balloon with Covering Material

b) Inflated Textured Balloon with Covering Material

Figure 4.16. Dilating Fenestrated Mesh Attachment, Prior to Implant.
To improve the implantation, removal, and ability to reposition the attachment, the textured balloon was partially covered with strands of monofilament. When the balloon is deflated, the monofilament strands prevent the attachment from gripping the bowel lumen. When the balloon is inflated, the monofilament strands are forced to spread out, exposing the texture material and enabling the attachment to grip the bowel wall.

have a circular array of holes through which the elastic cord is placed. When the balloon is deflated (Figure 4.16a), the function of the cords is to prevent the bowel lumen from making contact – thus enabling the attachments to be implanted, repositioned, and removed safely with ease. When the balloon is inflated (Figure 4.16b), the spacing of the elastic cords becomes less dense, allowing the tissue to make contact with the textured balloons and enabling the attachments to transfer load effectively.

To validate this functionality and evaluate the reliability and safety of using these attachments, a one week *in vivo* experiment was conducted where the attachments were cycled between their inflated and deflated states. While inflated, the balloons were separated by a reciprocating linear hydraulic device to apply tension on the small bowel. After several hours of applying tension, the balloons were deflated and the reciprocating hydraulic device was retracted for several hours to allow the bowel to relax and to reduce the risk of the attachments perforating the tissue. This cycle of tensioning and relaxing the small bowel segment was repeated for 8 hours a day over the course of one week.

Results from the one-week *in vivo* study indicated that the attachments were a success based on the health of the tissue and the attachment performance observed at the explant. One major concern with their use was that the texturing material would become saturated with debris over time, greatly reducing their attachment performance. To evaluate this failure mode, the attachment and detachment forces were evaluated at the explant with a load sensor. With the balloons of each attachment deflated, the device could move though the bowel lumen with ease, with the force required to initiate motion being measured at approximately 120 gf (value is for both attachments). With a single attachment engaged, the measure force exceeded 450 gf, saturating the measurement system. Although the texturing material appeared to be potentially clogged, the attachment performance was no less than that at the start of the implantation period. The other concern associated with the longer term use of these attachments was their effect on the health of the bowel wall, given the abrasive nature of the texturing material. Figure 4.17 shows the portion of bowel tissue that the attachment was in contact with for the duration of the implantation. Although parallel line imprints from the monofilament strands were observed and there was mild tissue inflammation, the tissue was in good health and had an intact mucosal lining.

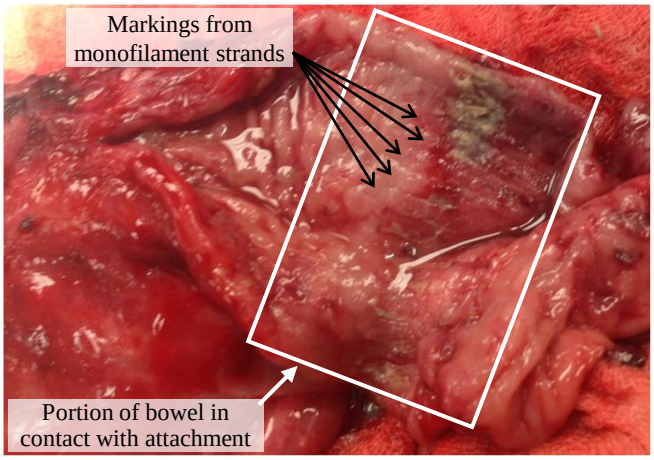


Figure 4.17. Effect of Attachment on Tissue Health.
At the explant surgery, the portion of the bowel tissue where the attachments made contact had markings from the monofilament strands and mild inflammation. Despite this, the health of the tissue appeared good because the mucosa was grossly intact and there were no perforations or tears.

4.3. Comparison of Attachment Approaches

The broad range of experimentally evaluated attachment concepts are shown in a chart for comparison in Figure 4.18, which categorizes the attachments based on their health and safety risk, and shows the attachment and purposeful detachment abilities of each attachment simultaneously. The health risks are qualitatively described as 1, the attachments are unlikely to cause a surgical complication, 2, there is some potential for surgical complication, and 3, there are expected serious surgical complications such as bowel perforation or ischemia. The dilation approaches are categorized as having the least health risk because there usage does not require any surgical manipulation of the bowel, and because they distribute their applied pressure evenly, the risks of bowel perforation and/or ischemia are low. The binding/kinking, clamping, and the suture approaches all require surgical manipulation of the small bowel. Therefore, they present a greater potential for surgical complications than the dilation approaches. Both the impingement and adhesion approaches pose likely surgical complications related to bowel ischemia and subsequent perforation. The starting and ending positions of the vertical bars labeled with the attachment concepts indicate how well each approach attaches and purposefully detaches for implantation and removal. For example, the "dilation (smooth)" approach failed (indicated by the "X") to work "acutely well (doesn't slip at loads exceeding 200 gf)" while inflated, but "slips freely" when deflated. This approach was not tested beyond an acute *in vivo* study, so its ability to attach "well

for up to one week" was not tested. All other attachment approaches can be read similarly from this chart.

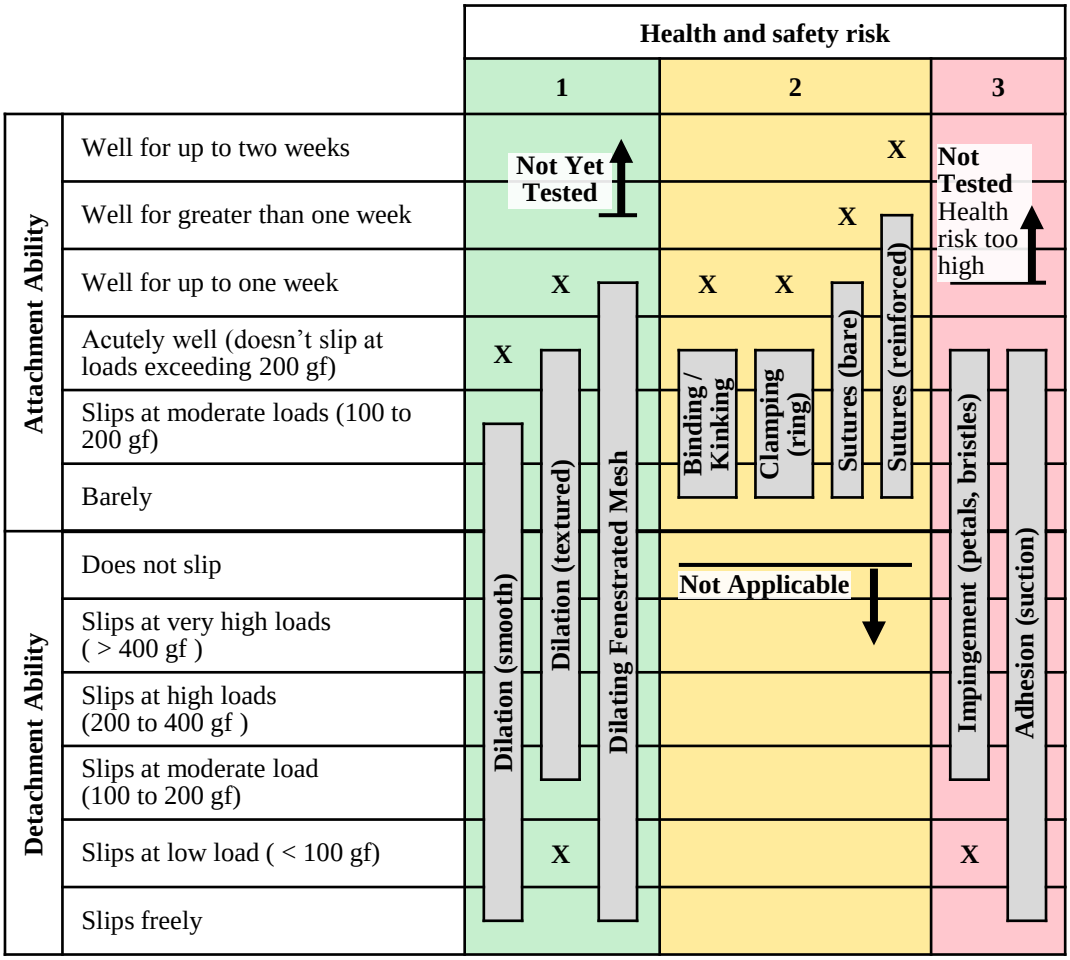


Figure 4.18. Comparison of Evaluated Attachment Approaches.

The attachment and detachment performance of the attachments, grouped by health and safety risk, is shown. Ideally, the attachments demonstrated strong attachment performance to induce tissue growth, and strong detachment performance to facilitate implantation, removal, and purposeful reposting. The total height of the bar for each attachment illustrates the sum of attachment and detachment performances. The health and safety risk ratings were given on a scale from 1 to 3, where 1 is the safest rating. Qualitatively, a rating of 1 indicates that the attachment approach is unlikely to cause bowel ischemia or perforation, and the attachment does not require any components to pierce through the tissue. A rating of 2 indicates that there is a moderate concern of bowel ischemia or perforation, or the attachment requires components to pierce through the tissue. Lastly, a rating of 3 indicates that the risk of ischemia or perforation or likely to occur if the attachment is implanted for more than one day. Xs indicate where the attachments were evaluated but did not achieve the attachment or detachment performance. Based on its safety, detachment performance, and attachment performance, the Dilating Fenestrated Mesh showed the most promise, although more experiments are required to evaluate its performance in trials exceeding one week.

Given the desired performance of being able to both attach and detach from the bowel lumen safely, the best candidate attachment approach is the Dilating Fenestrated Mesh. This is because the attachment was able to apply more the 200 gf reliably in experiments lasting up to one week, easily slid along the bowel lumen when detached, and posed little risk of bowel ischemia and/or perforation. However, their performance has not yet been evaluated in experiments exceeding one week, like the suture-based approaches. Despite this, the further experimental evaluation (beyond one week) of this approach is strongly supported by these initial results.

4.4. Conclusion

To investigate clinically relevant attachment approaches for supporting the development of enterogenesis devices to correct short bowel syndrome, a broad range of attachment approaches were conceptualized, fabricated, and evaluated in a series of *ex vivo*, acute *in vivo,* and longer term *in vivo* experiments with porcine animal models. The series of experimental studies confirmed the reliability issues of suture-based attachment approaches for small bowel tissue and identified the failure modes and health risks associated with each attachment approach.

Compared to other tissue attachment approaches in this study, the Dilating Fenestrated Mesh demonstrated the greatest promise. The approach demonstrated its ability to apply high tensile load on the small bowel without causing ischemia at the attachment/tissue interface in an experiment lasting one week. The approach also demonstrated its ability to traverse the small bowel freely. These performance capabilities have the potential to enable minimally invasive surgical methods that reduce the risk of surgical complications, lower the cost of treatment, minimize scarring, and shorten the recovery time.

The safe attachment and detachment of soft tissue to a foreign body is a challenging but important problem with broad medical applicability. Possible applications for intraluminal attachments beyond the treatment of SBS include the treatment of long-gap esophageal atresia, suture-less or low suture tension end-to-end anastomoses, improved mobility of endoscopic devices, and improved stent migration prevention. A currently practiced method for treating long-gap esophageal atresia, a condition where a segment of the esophagus is absent, is to apply tension to the two ends of the esophagus with traction sutures that are manually tensioned to induce esophageal growth and close the gap [13], [14]. Although the method is promising, a reported complication is that the sutures sometimes cut through the tissue. Therefore, the use of an

intraluminal attachment may be able to overcome this complication. Another possible use of intraluminal attachments is to provide traction for creating suture-less or low suture tension end-to-end anastomoses, which could help prevent leakage, tearing, and maintain the patency of the connection. The mobility and robustness of endoscopic devices may also be improved with the use of non-permanent intraluminal attachments. In a manner identical to double balloon endoscopy, endoscopes equipped with actuated non-permanent attachments may be guided along the GI tract more easily than with a traditional endoscope. Furthermore, the results of the attachment studies may be used to develop stents with improved resistance to migration.

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CHAPTER FIVE. DEVELOPMENT OF A CLINICAL DEVICE FOR TREATING SHORT BOWEL SYNDROME

Short bowel syndrome is an often lethal medical condition characterized by the malabsorptive state of a patient who was born with intestinal atresia or has undergone massive small bowel resection to treat intestinal pathologies. The condition is challenging to manage and treat because of complications associated with parenteral nutrition, surgical bowel restructuring techniques, and transplants. As a result, mortality rates associated with SBS are as high as 38% [1,2]. To provide an alternative to long-term parenteral nutrition reliance and surgical bowel lengthening, this dissertation explored technological approaches for a promising and novel treatment method of short bowel syndrome based on mechanotransductive enterogenesis.

Chapter Two established the feasibility of the mechanotransduction-based approach in clinically relevant animal models. To achieve this, the Curved Hydraulic Device was developed and used to induce large net growth of porcine small bowel. In a series of four *in vivo* studies, tissue expansion factors (final segment length divided by initial segment length) ranged from 1.6 to 2.2X, which is comparable to the lengthening factors achieved by the Bianchi and STEP bowel lengthening procedures. The grown tissue health was compared to control segments of tissue by evaluating tissue histology, morphology, barrier function, and epithelial cell proliferation, suggesting the true growth of healthy functioning bowel. Additionally, these studies have produced the first reported evidence of an increase in mesenteric vascularity to support the lengthened small bowel [3], further establishing the potential of the treatment approach. Chapter Three built upon this result and developed the treatment method with the Instrumented SMA Driven Ratchet by comparing different tissue expansion strategies, exploring the upper limit on how quickly small

bowel can be safely grown, and determining the safe range of tensile loading that can be applied to the tissue.

For clinically relevant devices, greater design constraints are present compared to devices for research. The most important differences are the need to be able to implant the device in a continuous portion of the small bowel (by non-invasive surgical techniques) rather than within an isolated segment, the greater constraints on the form of the device, greater lengthening capabilities to enable the treatment of severe cases of SBS, and an enhanced emphasis on device safety features including applied tensile load measurement, displacement control, and displacement measurement. While the Curved Hydraulic Device and the Instrumented SMA Driven Ratchet were critical for laying the foundational knowledge necessary for the development of a clinically relevant device, they do not fulfill the aforementioned clinical design constraints and considerations. The Curved Hydraulic Device was useful for inducing large net and high expansion factor growth, but the device is not implantable in continuous small bowel because its large outer diameter would likely cause bowel obstruction. Furthermore, the length and rigidity of the extended device would be too great to fit into the peritoneal cavity of some patients. The tissue expansion capability of the device is approximately 2 fold, which may serve a large percentage of SBS patients. However, if the outcomes of patients receiving the Bianchi and STEP procedures can be extended to bowel lengthening by mechanotransduction, approximately 60% of patients would not be able to wean from TPN following treatment with the Curved Hydraulic Device. Lastly, the Curved Hydraulic Device was not instrumented and there was little control of the device displacement, possibly leading to complications such as bowel tearing from overextension. Like the Curved Hydraulic Device, the implantation of the Instrumented SMA Driven Ratchet into a continuous bowel segment would also likely lead to bowel obstruction because of its outer diameter, and the length and rigidity of the extended device would not fit in some patients. The linear form of the device would cause extraneous tension on the mesentery during the distraction period, possibly causing mesenteric defects. Also, the tissue expansion capability of the ratcheting mechanism is 50%, which would thus serve a much smaller patient population than the Curved Hydraulic Device. Both the Curved Hydraulic Device and the Instrumented SMA Driven Ratchet are examples of *extension* devices, an approach category (among six others identified in this chapter) which is fundamentally not as well-suited to induce high net growth compared to other approaches. The enterogenesis devices used in prior research by other groups do not fulfill the clinical design constraints and

considerations either. The Internal Screw Device [4] is an extraluminal device designed to attach to the outside of a continuous bowel segment with sutured tissue couplers. Although the ability to grow a continuous segment of small bowel is clinically advantageous, the implantation of the device requires an invasive laparotomy, and the suture-based attachment approach is not reliable and requires piercing the remnant bowel. The External Screw Device [5] and Intraluminal Spring [6] are intraluminal devices that are designed to attach by end abutment, an unfavorable attachment approach that precludes non-invasive implantation methods, requires isolating the grown bowel segment, and requires bowel anastomoses that result in discarded small bowel tissue.

This chapter presents the development of a bowel extension device whose design focuses on clinical relevance rather than the enablement of research studies. Changing focus from research to clinical application required a full design cycle, starting with reassessing medical needs, producing a wide range of conceptual approaches, and downselecting to a single approach and embodiment. The selected embodiment was the Reciprocating Linear Hydraulic Device from the payout branch of the conceptualization tree, which was designed to be compatible with the Fenestrated Dilating Mesh attachment approach (most promising attachment from Chapter 4). The remainder of the chapter describes the design, prototype, fabrication, and *in vivo* validation of the Reciprocating Linear Hydraulic Device. The device presented in this chapter represents a large step forward in the development of a clinically relevant devices for correcting SBS for two key reasons. One, the device architecture has the potential to enable minimally invasive implantation and removal surgeries, greatly reducing the cost, recovery time, chance of surgical complications, and improving the overall quality of patient care. And two, the device can induce high net bowel growth within the limited space of the peritoneal cavity, potentially enabling the treatment of very severe cases of SBS in infants and children.

5.1. Design of Expansion Approach

To take the next step from research relevant devices to clinical, a traditional design process was used to identify the best expansion approach with the assumption that the Dilating Fenestrated Attachment approach from the previous chapter would be used. The design process steps were to develop selection criteria based on medical needs, organize and develop new expansion mechanism classes into a conceptualization tree, systematically compare the potential of each class

of mechanisms using a Pugh Chart, downselect to a single class of mechanisms, and design a detailed embodiment of the mechanism within the down-selected class.

5.1.1. Development of Selection Criteria

The development of selection criteria was driven by the additional design considerations and constraints for clinical relevant enterogenesis devices compared to research enabling devices, which include the ability to implant the device in a continuous portion of the small bowel (by non-invasive surgical techniques), greater constraints on the form of the device, greater lengthening capabilities to enable the treatment of severe cases of SBS, and an enhanced emphasis on device safety features including applied tensile load measurement, displacement control, and displacement measurement.

In a clinical setting, there are many benefits to implanting in continuous bowel by non-invasive surgical techniques. The key benefit of implanting in continuous bowel is that no anastomoses are required at the implant or explant surgery. Small bowel anastomoses should be eliminated because they present a risk of bowel obstruction and enteral content leakage, reduce the sterility of the implant and explant surgeries by exposing the bowel lumen to the surgical field, and most importantly, require significant lengths of small bowel to be discarded at the explant surgery in order to place the grown tissue segment back into the continuous GI tract. In contrast, implanting and removing the enterogenesis device by non-invasive techniques hastens the recovery period, and reduces scarring, medical complications, and costs. To achieve this, the device-to-tissue attachments should traverse the small bowel readily during the device implantation and removal, but must also be able to reliably transfer load to the bowel during the distraction period.

To implant in a continuous segment of the GI tract by non-invasive surgical techniques, reduce extraneous loads on the mesentery, and prevent bowel injury during device implantation/removal and expansion, many design parameters need to be considered that are related to the device form. These parameters are:

1. Length, rigidity, and curvature

   The length, rigidity, and curvature of an enterogenesis device are coupled parameters in the context of device maneuverability through the GI tract. For example, if the device length is very short, it may still be implantable through the upper GI tract even

if it is rigid and straight. Likewise, long devices must have some flexibility to be maneuvered through the upper GI tract. The maximum length of a device, regardless of implantation and removal procedure, is also limited by the size of the patient's peritoneal cavity and by the extent that the device induces stress in the mesentery supporting the bowel. Because the mesentery radially pulls on the bowel, giving it its curvature, long and straight devices place significant stress on the mesentery. To reduce mesenteric stress, long devices can be curved to mimic the natural curvature of the bowel, or simply shortened. In an unpublished study at the University of Michigan, the peritoneal cavity size of a characteristic one year old child was estimated by creating a three-dimensional reconstruction of the cavity from CT scans. The result of this study showed that approximate width and height of the cavity was 15 cm and 17 cm, respectively.

2. Diameter

   In general, the outer diameter of an enterogenesis device must be limited such that the device fits within the diameter of the relaxed bowel lumen. However, a more restrictive requirement exists for enterogenesis devices designed to be implanted in continuous bowel because the flow of enteral contents must not be obstructed by the device. To eliminate the risk of device-related bowel obstruction, which can lead to bacterial overgrowth and a cascade of further medical complications, both the device length and outer diameter should be limited in order to reduce the resistance of enteral content flow.

3. Proximal and Distal Bowel Tissue Interface

   The proximal and distal bowel tissue interfaces of enterogenesis devices need to be carefully designed to reduce the potential risk of bowel ischemia on either end of the device. This is because the manner in which the tissue drapes around the device can lead to sharp bends in the tissue that lead to ischemia and perforation.

4. Local Feature Contours

   Local enterogenesis device features that interface with the bowel wall must be contoured such that they do not induce bowel ischemia. The ischemia risk of uncontoured features is coupled to the device outer diameter, because as the outer diameter increases, the device must become more contoured to prevent ischemia. This consideration is particularly pertinent at the tissue attachment locations of the device, which often have the greatest outer diameter.

To design a clinically relevant enterogenesis device, the most important functionality of the device is to induce small bowel growth by an amount that is sufficient to wean the patient from parenteral nutrition. While critical for designing the device, setting the target net and/or expansion factor of the expansion mechanism is complicated by the fact that there is no one solution that fits all. While one patient may respond to a 20% increase in bowel length, another may require much more bowel lengthening to wean from TPN. To estimate a reasonable target net and factor expansion for the design, the outcomes of lengthening small bowel by surgical techniques were reviewed. Both procedures are discussed in Chapter One. In a 20-year single institution (Children's Hospital of Pittsburgh) retrospective study on the outcomes of patients receiving the Bianchi procedure [7], a surgical technique that doubles a length of small bowel, 10 out of 19 patients did not undergo any further surgical lengthening or bowel transplant. While 7 of those 10 patients weaned from parenteral nutrition (with 5 to 26 cm of remnant bowel), 3 died (with 9 to 15 cm of remnant bowel). Overall, despite doubling the length of their remnant small bowel, 12 (63%) patients did not wean from the procedure (9 patients required rescue by small bowel transplant and 3 patients died). Outcomes for STEP procedure patients are similar. In a study at the Children's Hospital of Boston [8], only 6 out of 16 patients who received the STEP procedure, resulting in a mean small bowel lengthening of 91 ± 38%, weaned from parenteral nutrition (62% did not wean). With either procedure, doubling or nearly doubling the length of remnant small bowel was not sufficient to wean more than half of the patient population. Thus, to improve patient outcomes with a clinically relevant device, at least 2 fold expansion capacity is needed to produce results similar the surgical lengthening procedures. However, because more than 60% of patients were not able to wean from parenteral nutrition in either study, greater than 2 fold expansion is the goal.

The control and measurement of the tissue expansion and applied tensile load are important safety features of a clinically relevant enterogenesis device for preventing tissue overextension and/or exceeding safe limits of the applied tensile load. The application of small bowel tension is limited by the risk of ischemia [9], a complication which can lead to bowel necrosis and perforation. This is a serious issue for SBS patients, because necrosed bowel tissue is no longer viable and must be surgically removed, worsening the severity of their condition. Additionally, bowel perforation leads to sepsis, a life-threatening complication caused by severe infection. To reduce the risk of overextending or applying too much load to small bowel tissue with enterogenesis devices lacking force instrumentation, the treatment regimen can be set to expand

the tissue at a very slow and conservative pace. However, this will not prevent bowel overextension with certainty, and leads to a longer than necessary treatment duration, increasing the risk of complications, the length of hospitalization, and the cost of care.

With these aspects of the design considered, selection criteria for the expansion mechanism of the clinically relevant device were identified in collaboration with pediatric surgeons specializing in the care of SBS patients at the University of Michigan and by extensive experience with *in vivo* experimental studies using the Curved Hydraulic Device and the Instrumented SMA Driven Ratchet. Ultimately, eleven criteria were identified and are defined below.

1. Does Not Injure Bowel While Implanted

   This criterion concerns the propensity of the device to cause bowel ischemia or perforation during the distraction period. The risk of bowel injury relates to the device form, and device force/displacement instrumentation and control.

2. Safety of Implantation and Removal

   This criterion relates the risk of mechanically injuring the bowel during the implantation and removal of the device by causing bowel perforations and/or tears. This risk is related to the device form and attachment approach.

3. Accurate Expansion of Tissue Control

   This criterion relates the ability of medical personal to accurately expand the bowel tissue by a predetermined amount.

4. Environmentally Robust

   This criterion relates to the robustness of the device performance to the time-varying loading environment, the device sealing to keep enteral contents out, and the device robustness to a time-varying anatomical environment.

5. Implantable in Continuous Bowel

   This criterion relates to whether a device is implantable in continuous bowel or must be implanted in an isolated segment.

6. Secure Attachments

   Many attachments work well acutely. This criterion relates the ability of an attachment to have reliable performance on the timescale of weeks.

7. Bowel Tension Monitored in Real-Time

   This criterion relates to the ability of medical personal to have a real-time measurement of the applied bowel tension available during treatment, an important diagnostic for preventing bowel injury and informing the tissue expansion protocol.

8. Compact Size

   This criterion relates to the overall size of the enterogenesis device.

9. High Growth Factor

   This criterion relates to the ability of the enterogenesis device to induce high fold growth, which is related to the net expansion capacity of the device as well as its unextended length.

10. Net Bowel Growth Monitored in Real-Time

    This criterion relates to the ability of medical personal to have a real-time measurement of the net bowel growth.

11. Extraneous Loads on the Mesentery Avoided

    This criterion relates to the interaction of the device form with the mesentery. Long, rigid, and straight devices cause extraneous loads on the mesentery at implant, while short, flexibility, and/or curved devices allow the mesentery to relax.

5.1.2. Conceptualization of Expansion Mechanisms

To meet the demanding criteria, a full conceptualization study was conducted resulting in seven distinct approaches depicted in the concept tree (Figure 5.1). The seven major approaches differ fundamentally in their architecture, operation, and/or implantation location, and have important advantages and disadvantages relative to each other. The approaches include Extension, Payout, Track, Feed-In, Motility, Secondary Growth, and Field-Induced. Although the feasibility of Motility, Secondary Growth, and Field Induced approaches was questionable, they are included in the concept tree for completeness. A brief explanation of each approach is given.

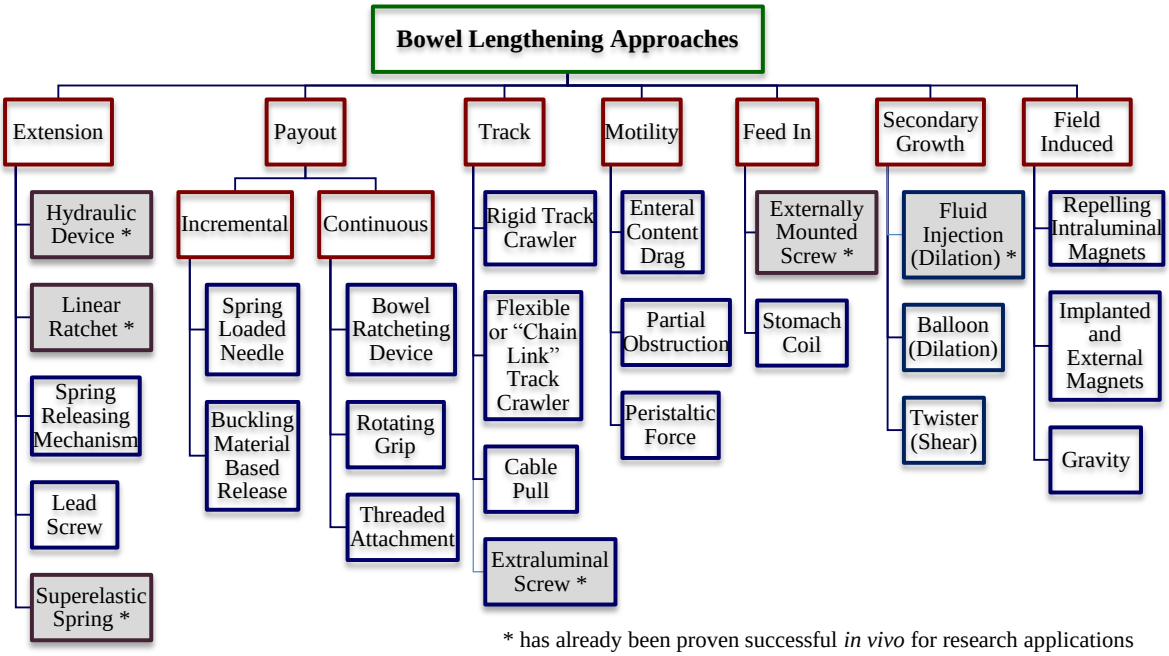


Figure 5.1. Conceptualization Tree.

Seven unique enterogenesis device conceptual approaches were identified in the design process. Six of the concepts have been previously used in enterogenesis studies. The extension concept branch includes the Linear [10] and Curved Hydraulic Devices, the Instrumented SMA Driven Ratchet, and the Superelastic Spring [11]; The track approach includes the External Screw used in the rabbit study [4]; the feed-in branch includes the externally mounted screw used in studies with rats [5,12,13]; and the secondary growth approach includes dilation by fluid injection [10].

5.1.2.1. Extension

Extension devices are those where the device is designed to lengthen one time within a segment of small bowel to apply tension to the bowel through attachments on the opposing ends of the device. By definition, Extension devices can only extend and cannot be retracted or reset during their implantation. The Intraluminal Spring [6,11,14], Linear Hydraulic Device [10], Curved Hydraulic Device, and Instrumented SMA Driven Ratchet are all examples of this approach, because they expand once while implanted and the body of the device remains within the segment of small bowel during the extension. Thus, the percent expansion and net expansion of the grown tissue segment closely matches that of the device. Compared to other expansion approaches, Extension devices are readily implemented, which is why many prior enterogenesis devices have taken this approach. However, the approach is not well-suited for inducing high net small bowel lengthening because their expansion capability is limited by the peritoneal cavity of the patient and their remnant small bowel length. Because Extension based mechanisms

monotonically expand during their implantation, both end-abutting and non-end-abutting attachments may be integrated into devices of this class.

5.1.2.2. Payout

Payout devices, which have been subcategorized into incremental and continuous approaches, have the potential to grow very large lengths of bowel because the net growth of the small bowel is not limited by the peritoneal cavity of the patient or their remnant bowel length. This is because Payout devices are able to selectively attach and detach from the bowel wall and do not expand monotonically throughout the implantation period. Rather, incremental payout devices cycle between expanded and contracted states while continuous payout devices do not increase in size whatsoever. Incremental payout devices operate by repeating four stages:

1. the device is retracted and the attachments are engaged in the tissue,
2. while attached, the device extends to induce bowel growth,
3. the device attachments are disengaged from the tissue, and
4. the device returns to its retracted state, the attachments are reengaged, and the process is repeated.

Ideally, as the device expands in stage two, it is tensioning a shorter length of the previously distracted segment of bowel, because part of the previously tensioned and grown bowel from the previous cycle has "paid out" in stage 4. Continuous payout devices remain attached to the small bowel and continuously apply tension with a rotating attachment. Unlike all prior reported enterogenesis devices, a key advantage of the general payout approach is that the length of bowel grown is not limited by the initial length of remnant small bowel, by the device size, or subsequently, by the size of the peritoneal cavity of the patient, because a compact device can continue to payout bowel until a physiological limit is reached or sufficient bowel growth has be induced. Because the incremental payout approach requires the use of selectively active attachments, it is not compatible with the end-abutting attachment approach and it is challenging to measure the net bowel lengthening.

5.1.2.3. Track

Track devices utilize two initially adjacent bowel attachments which are fixed to an intraluminally implanted flexible or rigid track, which is located completely within a segment of

the small bowel. Bowel growth is induced as one or both attachments move apart along the track, thereby inducing load on the tissue. This approach is advantageous for producing high expansion factor bowel growth, because the attachments may initially be very close, even though the total length of grown bowel is limited by the length of the track. An important disadvantage of this approach is that the applied bowel tension would be difficult to measure along a curved track, because the load of the tissue would include tensile and bending components. Unlike the extension approach, track devices are not compatible with the end-abutment tissue attachment approach because the track cannot pass through a segment of bowel that is surgically closed.

5.1.2.4. Feed-In

Feed-In devices are very similar in nature to Track devices, with the major difference being that the component acting as the track is not completely contained within the small bowel initially. The track of the Feed-In device may have components that are initially external to the patient or within the stomach of the patient. An example of this approach is the External Screw Device used in the rat studies [5,12,13], because the screw was initially external to the bowel lumen of the animal model. Because of this, both end-abutting and non-end-abutting attachments may be integrated into devices of this class. Another difference with Track devices are the kinematics of the attachments relative to the track component. The track component of a Feed-In device moves through the attachments, while for Track devices, the attachments move along the track component. Like the Track approach, the Feed-In approach can induce high expansion tissue growth because the length of the initial bowel segment may be very small.

5.1.2.5. Motility

Motility based devices rely on the healthy motility of the small bowel, and transmit forces on the tissue from either the drag generated by the flow of enteral contents on a intraluminally implanted object and/or by the force generated by peristalsis. This branch of the conceptualization tree was considered for completeness of the design approach, but Motility based approaches suffer from major fundamental drawbacks. The first of which is that the two subclasses, enteral content and partial obstruction, rely on the healthy transit of enteral contents through the bowel lumen. However, SBS patients have limited to no enteral nutrition in their diet. Thus, there will not likely be enough enteral content passage to create a drag force. The peristaltic force subclass also relies on the healthy function of peristalsis in SBS patients. However, because large portions of SBS

patient small bowel is dilated, the effect of peristalsis on intraluminal objects is likely to be minimal.

5.1.2.6. Secondary Growth

Secondary Growth devices rely on the concept that the non-longitudinal application of load on bowel tissue will result in growth with a longitudinal component. For example, if bowel tissue is dilated with a balloon, the tissue growth will occur radially and have a longitudinal component. One implication of this approach is that after the device is removed, the dilated segment may be surgically tapered and lengthened with either the Bianchi or STEP procedure to increase the length of bowel. However, both restructuring procedures are associated with complications and the requirement of additional surgical procedures to correct recurrent dilation of the bowel [15]. Another non-longitudinal application of load would be to develop shear in the tissue through twisting. The result of twisting the tissue has not been experimentally evaluated, because there is a large risk of tearing the bowel mesentery.

5.1.2.7. Field Induced

Field Induced devices are non-actuated and rely on forces developed by gravitational or magnetic fields to create tension on small bowel segments and induce their growth. Like Motility, this branch of the conceptualization tree was considered for completeness of the design approach. To utilize gravity, a segment of bowel could be tensioned by attaching a weight to the remnant small bowel segment of an SBS patient. In this approach, the bowel is tensioned between the Ligament of Treitz (which attaches the duodenum to the diaphragm) and the distal (downstream) weight. This approach requires the patient to be upright and works only if the applied weight does not come to rest on an organ or become stuck within the peritoneal cavity. Another concept is to use magnets that are attached to a bowel segment and repeal each other. However, because the magnetic repulsion force scales with the square of the distance between the magnets, the tension applied to the tissue segment would decrease rapidly as the bowel tissue grows, resulting in only a small amount of tissue lengthening.

5.1.3. Downselection

To downselect among the approaches, a Pugh Chart (Figure 5.2) was developed with ratings for each approach against each selection criterion. The rating values are 1, 3, 6, and 9, where 1

		Conceptual Approach						
Selection Criteria	**Weight**	**Payout**	**Feed In**	**Extension**	**Track**	**Field Induced**	**Motility**	**Secondary Growth**
Does Not Injure Bowel While Implanted	10	6	6	6	6	6	6	6
Ease and Safety of Implantation and Removal	9.5	6	6	6	6	6	6	6
Accurate Expansion of Tissue Control	9	6	9	9	9	3	3	3
Environmentally Robust	8.5	6	6	6	6	9	9	6
Implantable in Continuous Bowel	8.5	9	6	6	9	6	9	6
Secure Attachments	8	6	6	6	6	6	6	6
Bowel Tension Monitored in Real Time	7.5	9	6	6	3	6	3	1
Compact Size	7	9	6	6	3	9	9	9
High Tissue Growth Factor (> 2)	5.5	9	9	6	9	3	3	3
Net Bowel Growth Monitored in Real Time	5	3	9	9	9	6	1	1
Extraneous Loads on Mesentery Avoided	5	9	6	6	6	9	6	9
	3.5	587	560	543	542	519	482	431
	Total Less Mean	63.3	36.3	19.79	18.3	-4.21	-41.2	-92.2

Figure 5.2. Pugh Chart of Expansion Mechanisms.
To inform the downselection of the seven conceptual approaches, a Pugh Chart was created and each of the conceptual approaches were rated on their ability to meet the selection criteria, where 9 indicates a strong ability to meet the criterion, and 1 indicates the it is unlikely for the conceptual approach to meet the criterion. The total score for each concept was calculated as the weighted sum of the scores, and the "total less mean" scores were calculated by subtracting the mean of the total scores from the total score for each concept.

means the approach will not likely work for meeting the selection criterion, 3 means the approach is not-well suited for meeting the selection criterion, a rating of 6 is neutral, and 9 means the approach is well-suited for meeting the selection criterion. Additionally, the importance of the downselection criterion were rated on a 0-10 scale by a committee of pediatric surgeons specializing in the care of SBS patients at the University of Michigan.

A discussion of the ratings for each differentiating criterion follows. "Does not injure bowel while implanted," "Ease and Safety of Implantation and Removal," and "Secure Attachments" were not considered to be differentiating criteria, because each approach can address the criteria similarly.

1. Accurate expansion of tissue control

   The Extension, Track, and Feed-In approaches were assigned 9s because when implanted, their attachments can be permanently fixed to the tissue, and the displacement of each expansion mechanism can be controlled. Although the Payout approach mechanism can have displacement control, Payout compatible attachments

must be able to act in attached and detach states. Thus, tissue is more likely to slip with attachments compatible with the Payout approach, and the approach received a neutral score of 6. The Field Induced, Motility, and Secondary Growth approaches are not well-suited for accurately controlling the expansion of tissue, because they are not displacement controlled architectures. They have been assigned 3s, because there is a possibility that they can be adapted to achieve some control of tissue expansion.

2. Environmentally robust

   The most environmentally robust approaches are Field Induced and Motility, both assigned 9s, because they are simple, passive, and have embodiments with no moving parts. Thus, although they may not be likely to work, they are also not likely to break. All other approaches are equal with regard to environmental robustness and were assigned 6s.

3. Implantable in continuous bowel

   By definition, Feed-In devices are not implantable in continuous bowel, because they feed into the bowel from outside. While they cannot by definition be implanted in continuous bowel, they can still be fully implantable devices that grow a segment of continuous bowel. Thus, the Feed-In concept was assigned a 6 with regard to implantability in continuous bowel. The Payout, Track, and Motility approaches were the best-suited approaches for this criterion and received 9s because they can be embodied by compact and flexible expansion mechanisms.

4. Bowel tension monitored in real-time

   The Payout approach received the only 9 for this criterion because Payout devices can be compact (load less affected by mesenteric stress) and linear (making the load on the bowel tissue as close to pure tension as possible). The Track approach was assigned a 3 because embodiments of the Track approach include long, curved and flexible tracks, making the load on the bowel tissue have non tensile components requiring complex instrumentation. The Motility approach was assigned a 3 because it would be difficult to attach a force sensor to the bowel wall and the passive drag-creating object. The Secondary Growth approach is unlikely to be able to be compatible with the ability to measure bowel tension because Secondary Growth devices do not directly apply tension loads. Thus, Secondary Growth was assigned a 1 for this criterion.

5. Compact size

   The Payout Approach is well-suited to be compact because the net growth of tissue that payout devices can induce is not limited by the stroke of the device, which is

coupled to device size. Thus, the Payout approach was assigned a 9. The Field Induced, Motility, and Secondary Growth approaches were also assigned 9s because they are simple to implement approaches can have compact embodiments.

6. High tissue growth factor (> 2X)

   The Payout, Feed-In, and Track approaches were assigned 9s because with each approach, the initial segment length of bowel can be very short. Thus, even moderate net amounts of bowel growth can result in high growth factors. The ability of the Field Induced, Motility, and Secondary Growth approaches to lengthen bowel by any amount is questionable, as the approaches were included in this design process only for completeness. Thus, these approaches were assigned 3s.

7. Net bowel growth monitored in real-time

   The Extension, Track, and Feed-In approaches are the best-suited for monitoring the net growth of bowel because they are compatible with permanent attachment approaches. Thus, they were assigned 9s. The Payout approach, which was assigned a 3, must use attachments that are more prone to slipping due to their requirement to attach and detach. Therefore, monitoring the net growth of bowel in real-time with payout-based devices would be much more difficult. The Motility and Secondary Growth approaches are unlikely to enable real-time measurement of net bowel growth because their embodiments attach to the bowel at one location and at least two references points are required for a growth measurement, and thus there were assigned 1s.

8. Extraneous loads on mesentery avoided

   The Payout, Field Induced, and Secondary Growth approaches are least likely to apply extraneous loads on the mesentery because they are most likely to be embodied by short devices. Thus, they were assigned 9s, while the other approaches were assigned 6s.

A total score for each approach was found by summing the products of each criterion weight and approach rating pair, and the difference in each total score from the mean of all approaches is plotted in Figure 5.3. Based on this results, the Payout approach is the clear leader because it was well-suited for most of the selection criteria. The main advantage of the Payout approach is that it is the only concept that is well suited for achieving a high growth factor while simultaneously being compact. Furthermore, because the device pays out tissue, the net growth of tissue is not limited by the stroke of the device. Instead, the only limitations to growth will be physiological, if

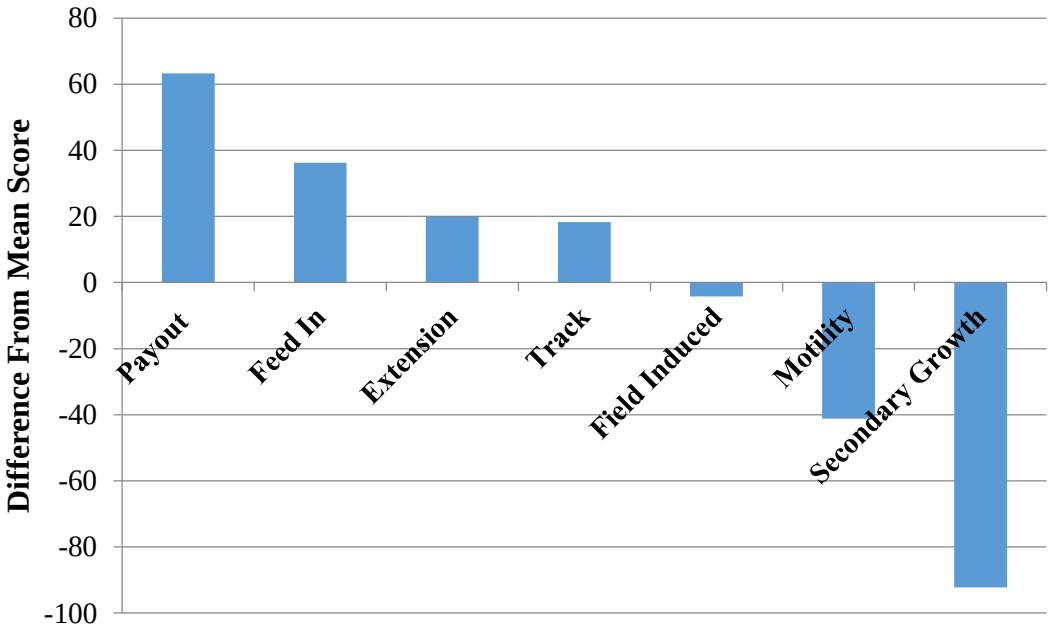


Figure 5.3. Concept Score Difference from Mean.
By plotting the difference of each concept score with the mean of the concept scores, the decision to downselect to the Payout approach in clear.

they exist, making the device capable of producing high tissue growth factors. The main disadvantage of the approach is that it would be difficult to measure the net bowel growth in real-time because the device pays out tissue, which becomes difficult to track once it is beyond the device.

5.1.4. Payout Expansion Mechanism

Two subclasses of payout devices have been conceptualized: the incremental payout device, and the continuous payout device. The main difference between the two approaches is that the incremental payout operation involves expanding and retracting the device cyclically and requires at least one attachment to disengage, reset, and slide easily through the bowel lumen, whereas the continuous payout operation continuously applies tension to the bowel with rotating attachments that never completely disengage.

The incremental and continuous payout approaches are rich with numerous possible embodiments. However, the most promising attachment approach, the Dilating Fenestrated Mesh (Figure 5.9), is only compatible with incremental approaches. The architecture and operation of

the downselected incremental payout approach, the Reciprocating Linear Hydraulic Device, is described below.

5.1.4.1. Architecture

The architecture of the Reciprocating Linear Hydraulic Device is shown in Figure 5.4. The concept consists an outer housing and an inner housing that displace relative to each other when

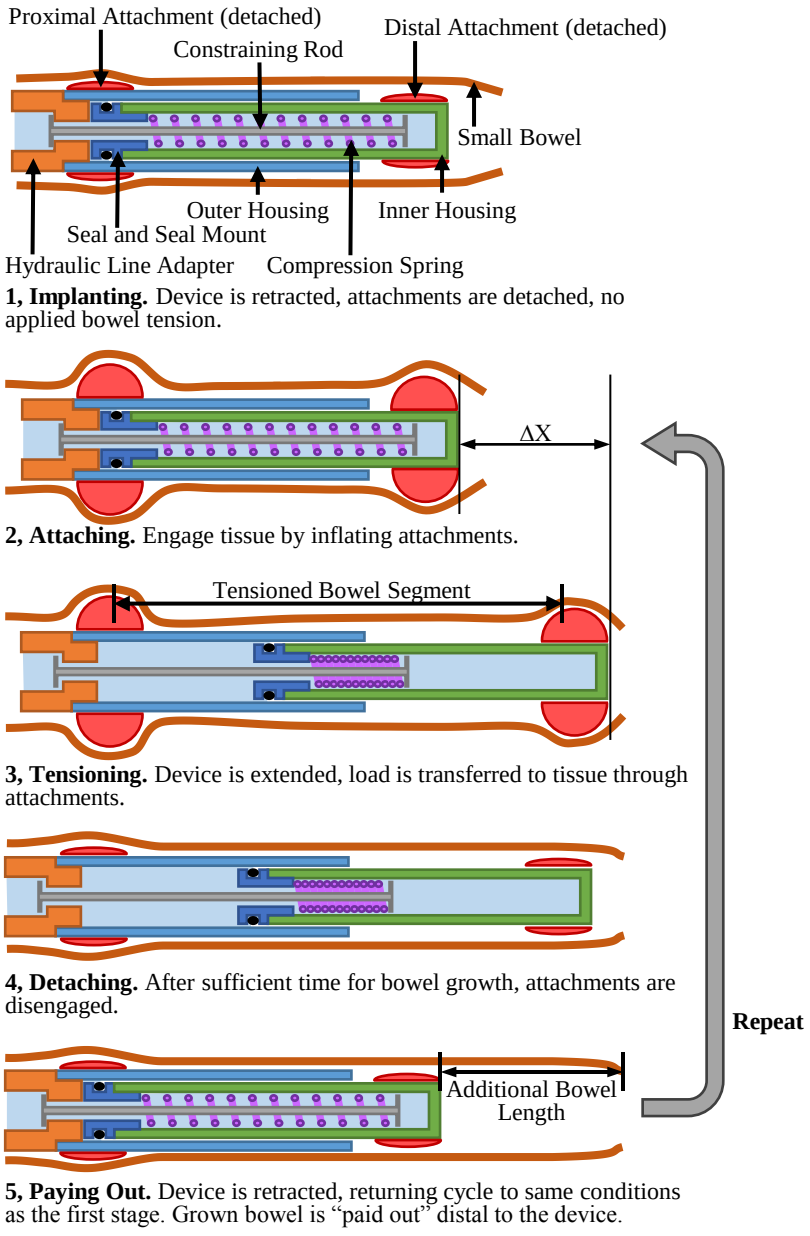


Figure 5.4. Architecture and Operation of Reciprocating Linear Hydraulic Device. The Reciprocating Linear Hydraulic Device is based on the Payout approach. By repeating the operation cycle, the length of tissue growth induced is limited by the number of times the device is cycled rather than the device stroke.

hydraulically driven, two attachments that are capable of gripping and releasing the bowel wall, a compression spring which retracts the device, a constraining rod that limits the motion of the inner housing relative to the outer housing, and a hydraulic line adapter. The hydraulic line connects to an external syringe from which water can be injected into the device. In addition to the hydraulic line, two pneumatic lines connect each attachment to external syringes to inflate and deflate the balloons.

5.1.4.2. Operation

The payout operation of the Reciprocating Linear Hydraulic Device with textured balloon attachments is described in five stages and illustrated in Figure 5.4. In the first, nominal, or "implanting" stage, the device is retracted and the attachments are deflated, disengaging them from the tissue. In the "attaching" stage, the attachments are inflated from external syringes through pneumatic lines, pressing the abrasive mesh material into the bowel lumen and thus gripping the tissue. In the "tensioning" stage, water injected from an external syringe through the hydraulic line enters the inner and outer housings of the sealed device, forcing the displacement of the inner housing relative to the outer housing. As more water is injected from the external syringe, the constraining rod and seal mount compress the spring until it reaches its solid length. At this point, further device expansion is not possible and the bowel segment between the attachments is tensioned. The expansion of the device and engagement of the attachments is maintained for a time sufficient to induce bowel growth prior to disengaging the attachments (venting the balloons to atmospheric pressure) in stage four, the "detaching" stage. Ideally at stage four, the bowel has grown and does not reduce in length when the attachments are disengaged. In the "paying out" stage, the pressure on the hydraulic line is reduced to atmospheric pressure and the compression spring retracts the device, leaving the additional length of tissue distal to the distal attachment. The completion of stage five returns the device to its nominal position, and the cycle is repeated multiple times during the distraction period of an implantation. Each time a cycle is completed, the amount of bowel growth induced is accumulated without the length of the device accumulating. Therefore, the growth of the small bowel is not limited by the constrained space of the peritoneal cavity or the remnant length of small bowel. This represents a very important advantage compared to the other conceptual expansion approaches for treating SBS. This advantage would not be possible without the ability of the attachments to disengage and reengage the bowel lumen.

5.2. Reciprocating Linear Hydraulic Device Prototype

From engineering drawings, a prototype of the expansion mechanism was fabricated and integrated with the Fenestrated Dilating Mesh attachments introduced in Chapter Four to enable *in vivo* experimental studies with the goal of demonstrating the payout approach to small bowel lengthening in porcine animal models. Prior to implanting the Reciprocating Linear Hydraulic Device into pigs, the performance of the device was successfully validated and the relationship between the input hydraulic line pressure and the expansion of the device was experimentally characterized on the benchtop.

5.2.1. Expansion Mechanism

The expansion mechanism, shown in section views in Figure 5.5, is a reciprocating single-stage linear hydraulic device. The prototype was fabricated by traditional milling operations with predominately corrosion resistant stainless steel components including the inner and outer housings, the compression spring, the E-style retaining rings, the 1/16 inch dowel rod, and the set screws. All other components were Delrin or nylon, and the O-rings were EPDM rubber. The motion of the inner housing relative to the outer housing is driven hydraulically with approximately 2 cc of water, expanding to a maximum displacement of 3.4 cm. As water is injected through the hydraulic line, the water flows through the luer lock adapter and the Delrin radial O-ring mount through which the 1/16 inch dowel rod passes, filling both the outer and inner housings with pressurized water. As the hydraulic pressure is increased, the compression spring approaches its solid height (0.86 in), stopping the motion of the inner housing relative to the outer housing. When the pressure from the hydraulic line is lowered, the compression spring retracts the device to its original length. Although the mechanism could retract without the compression spring by creating a negative gage pressure on the hydraulic line, this approach is not robust to friction from the seal because the return force would limited by the vacuum pressure to approximately 200 gf. Whereas the return force with the compression spring varies from approximately 1500 gf (full compression) to 1000 gf (device fully retracted). It should be noted that these forces act internally to the device, as they are largely transmitted from the spring through the dowel pin, and they do not act on the bowel.

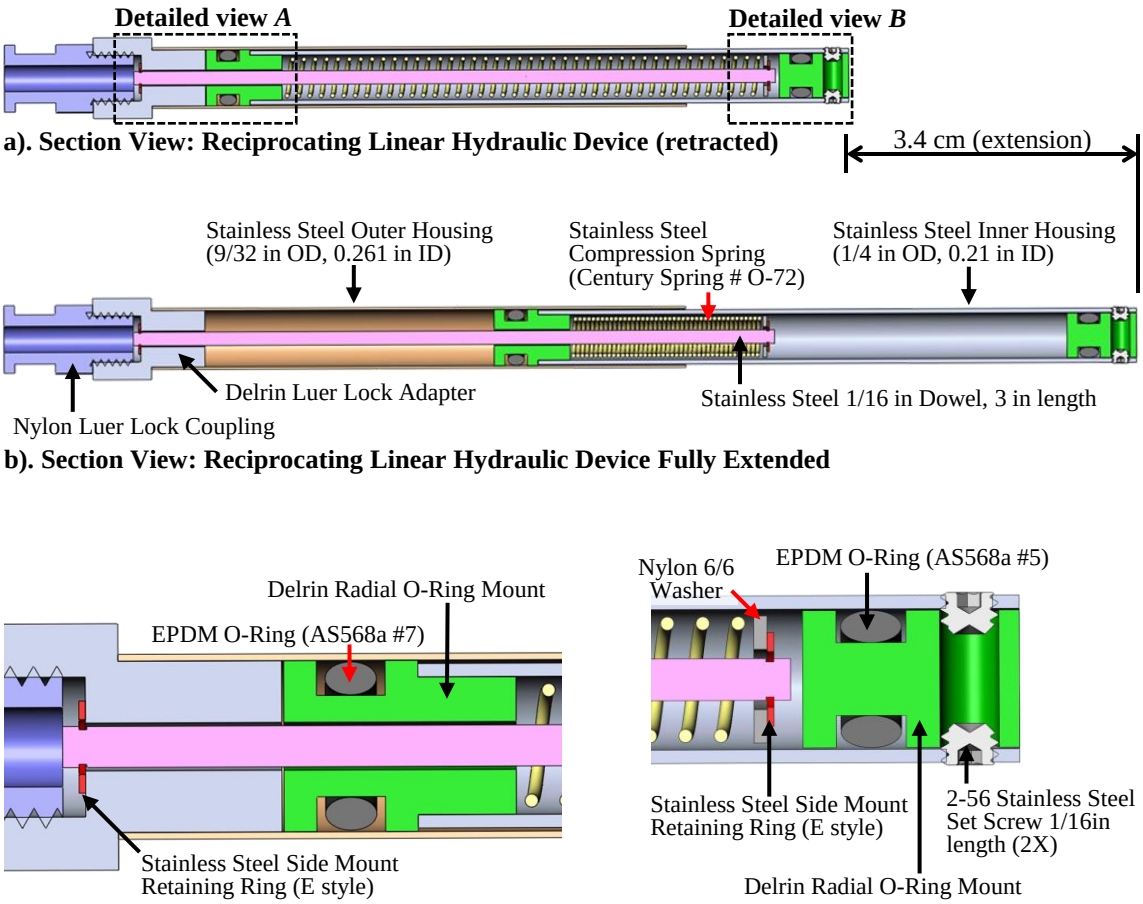


Figure 5.5. Section Views of Expansion Mechanism Prototype.

Section views of the Reciprocating Linear Hydraulic Device show how the device is sealed, how the device reciprocates, and how the stroke is limited. The O-ring seals (seen in c and d) prevent water from leaving the outer and inner housings of the device. Thus, as water is injected from the hydraulic line, the inner housing displaces, lengthening the device and compressing the spring. Once the compression spring reaches its solid height, further displacement of the inner housing relative to the outer housing is prevented by the 3 inch dowel pin in the center of the device. As the pressure of the working fluid is released, the compression spring returns the device to its original length.

The assembled expansion mechanism is shown in Figure 5.6 with the hydraulic line attached. Additionally, a mount for the distal attachment, not shown in Figure 5.5, is shown in Figure 5.6. The distal attachment mount was made from the same 316 stainless steel tubing as the outer housing and is 1.85 in (4.7 cm) in length, the same length as the attachments described in the following section.

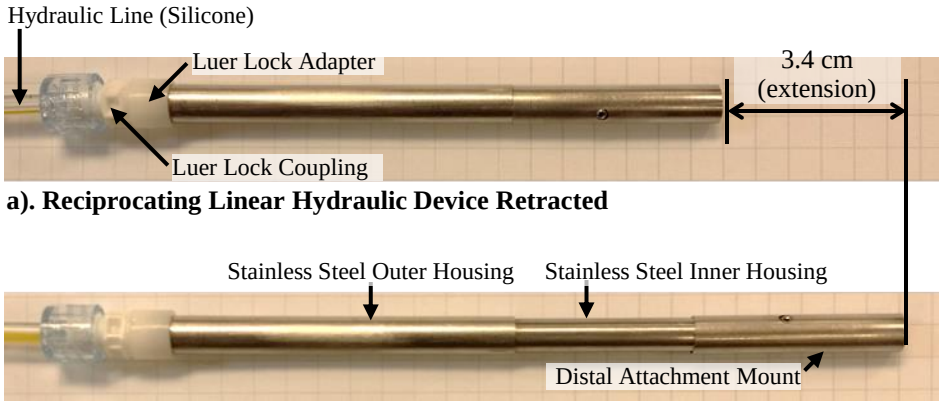


Figure 5.6. Expansion Mechanism.

The fabricated Reciprocating Linear Hydraulic Device is shown prior to its integration with the attachments.

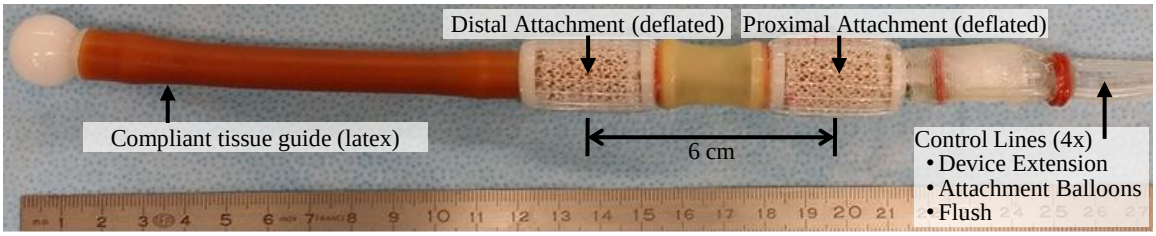
5.2.2. Expansion Mechanism Integration with Attachments

The extension mechanism was integrated with a distal and proximal tissue attachment having the capability to both attach and detach from the bowel wall, enabling the payout operation. Figure 5.7 shows the components of the integrated prototype prepared for *in vivo* experiments, which includes a compliant device extension made from 18 Fr latex tubing, the distal and proximal attachments, a thin silicone sheath held between the attachments, and 4 controls lines for the device extension (water), the flush (water), and the independently inflated balloons for the attachments (air).

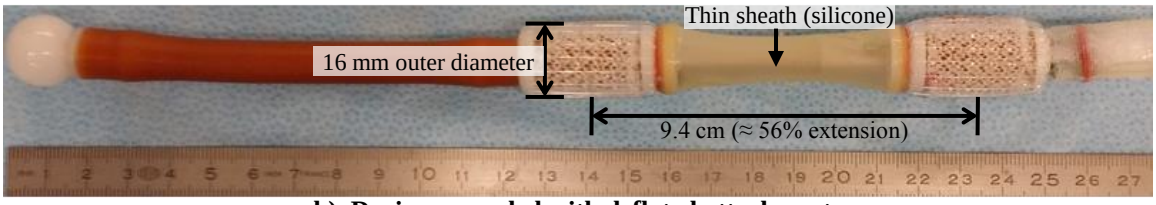
A detailed view of the inflated distal attachment is shown in Figure 5.9. Each attachment is composed of two machined Delrin filament guides, abrasive texturing material taken from a scrubbing sponge (Scotch-Brite "Dobie"), a balloon taken from a Foley catheter (Bard® BARDEX 30 Fr 5cc), and a single length of clear elastic monofilament. To assemble, the balloon is mounted directly on the extending mechanism, with the monofilament guides on each end, the abrasive material is positioned over the balloon and held in place by the monofilament line, which is threaded through the guides.

The compliant tissue guide was designed to enhance the way the bowel drapes around the device by preventing the tissue from kinking sharply around the distal end of the device. A silicon coated Delrin sphere (16 mm diameter) was placed at the end of the tissue guide to prevent bowel perforation by distributing the force on the tissue over a large smooth surface. The importance of

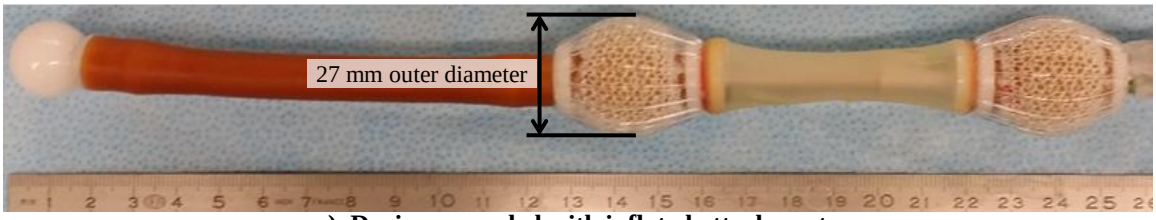
using a compliant tissue guide is illustrated in Figure 5.8, which shows how the tissue drapes around an enterogenesis device without a compliant tissue guide (Figure 5.8a) and how the tissue drapes around the Reciprocating Linear Hydraulic Device equipped with two embodiments of the compliant tissue guide (Figures 5.8b and 5.8c). Without the compliant tissue guide, the enterogenesis device shown in Figure 5.8a abutted a small area of the small bowel tissue, which caused an area of localized pressure and acute ischemia. To prevent this complication with the Reciprocating Linear Hydraulic Device, the distal end of the device was equipped with a single diameter compliant tissue guide, as shown in Figures 5.7 and 5.8b. Compared to the device without the compliant tissue guide, the single diameter compliant tissue guide greatly improved the perfusion of blood within the bowel tissue by distributing mesenteric tension over a greater area of bowel tissue. The design of the compliant tissue guide was improved by tapering the diameter



a). Device collapsed with deflated attachments



b). Device expanded with deflated attachments



c). Device expanded with inflated attachments

Figure 5.7. Prototype Integrated with Attachments.

The integrated prototype is composed of the Reciprocating Linear Hydraulic Device, distal and proximal tissue attachments separated by a thin silicone sheath, a compliant tissue guide, and a set of four silicone tubes connecting the device to external syringes. When the device is retracted, the thin silicone sheath prevents the bowel from pleating between the attachments, promoting the repositioning of bowel relative to the attachments. The compliant latex tissue guide prevents the bowel tissue from sharply kinking around of the device and becoming ischemic.

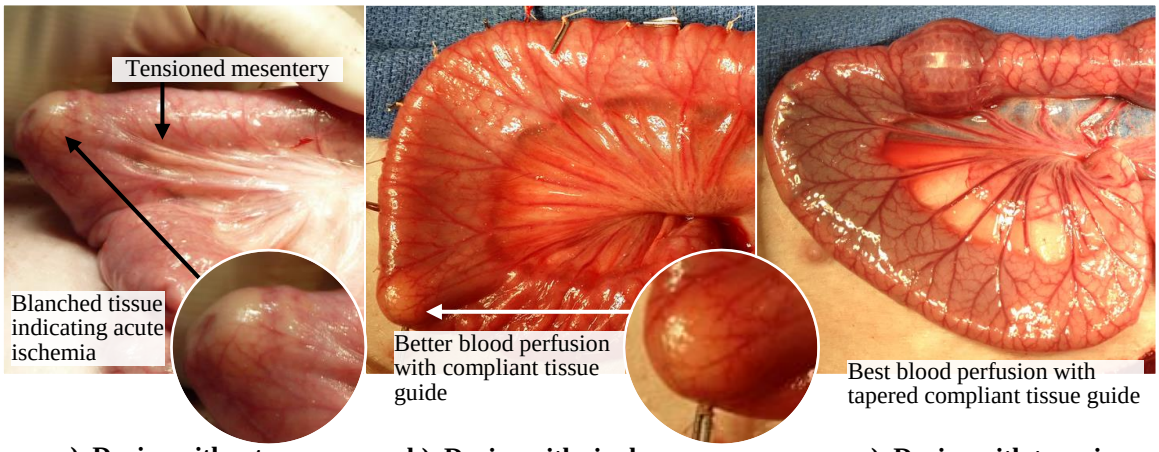


Figure 5.8. Compliant Tissue Guide.

A compliant tissue guide was integrated with the Reciprocating Linear Hydraulic Device to reduce the risk of ischemia related to the interaction of the tissue with the distal end of the device. In 5.8a, the enterogenesis shown does not have a tissue guide. As a result, tension in the mesentery caused a small area of the bowel tissue to become acutely ischemic. By transitioning from the rigid device to a single diameter complaint tissue guide in 8b, the perfusion of blood within the bowel tissue was better maintained. Using a tapering compliant tissue guide further improved on this result.

of the guide such that a smooth transition from the rigid device to the compliant bowel tissue was achieved. The tapering compliant tissue guide was fabricated by attaching a series of catheter segments with decreasing diameters end-to-end. The tapering embodiment of the compliant tissue guide provided the best performance with respect to preventing ischemia, as no blanching was observed in the tissue (Figure 5.8c).

The thin silicone sheath between the attachments was designed to prevent the tissue from pleating between the attachments when the device is retracted, encouraging the tissue to slide over the attachments in their deflated state. A flush line was included to help remove pleats from the tissue between the attachments. The flush is located between the attachments and under the silicone sheath, which has small holes in it to allow the flushed water to flow into contact with the bowel wall. Four silicone lines, which attach to the proximal end of the device, provide independent control of each attachment (two pneumatic lines), the flush line (hydraulic), and the line driving the displacement of the extension mechanism (hydraulic).

The total length of the device (excluding the lines) is approximately 26 cm, although when retracted the attachment-to-attachment distance is 6 cm. When the attachments are deflated, the maximum outer diameter of the device is 16 mm (5/8 in), which is expands to 27 mm when the

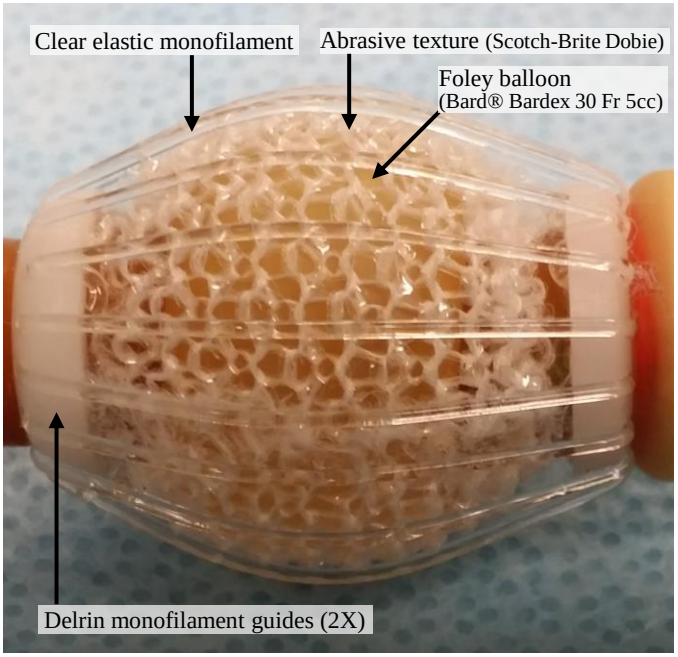


Figure 5.9. Detailed View of Attachment.
The distal and proximal attachments are composed of a balloon from a Foley catheter wrapped with an abrasive texturing material. To aid in the implantation, removal, and repositioning of the attachments (critical for the Payout approach), the abrasive material is partially covered with elastic monofilament strands woven through the Delrin guides. When the Foley balloon is deflated, the attachment slides through the bowel lumen with ease because the monofilament strands prevent the interaction of the tissue with the abrasive material. When the Foley balloon is inflated, the monofilament strands are forced to separate and the abrasive material is pressed into the bowel wall, achieving fixation.

attachments are inflated with 20 cc of air. The device extends by 3.4 cm when actuated by the hydraulic line with approximately 2 cc of water, displacing the midpoints of the attachments from 6 to 9.4 cm (56% expansion).

5.2.3. Benchtop Prototype Characterization

A benchtop characterization of the Reciprocating Linear Hydraulic Device was conducted to experimentally measure the pressure on the input syringe required to initiate the motion of the device, the pressure on the input syringe required to fully extend the device, the volume of inputted working fluid (water) corresponding to full extension, and to visually inspect the device for leaking at pressures exceeding normal operation conditions. The measurements of the required input water volume and pressure to achieve full device extension were a potentially useful diagnostic for evaluating the performance of the device while implanted (if a leak was suspected).

An experimental setup was created to measure the hydraulic line pressure and device extension simultaneously. To measure the pressure of the syringe, a "T" shaped fitting was introduced into the hydraulic line near the syringe and a pressure sensor (Freescale Semiconductor, MPX2200) was placed at one of the junctions. The other two junctions were for the syringe and the hydraulic line leading to the device. The extension of the device was measured with a laser displacement probe (Micro-Epsilon, OptoNCDT). The outputs of both sensors were read into LabVIEW by a DAQ (NI USB-6009) and calibrated based on each manufacturers' given calibration constants.

The experimental procedure consisted of the following steps:

1. To remove air pockets from the hydraulic line and device, flush hydraulic line with water before attaching it to the device
2. Mount the device relative to the laser displacement probe such that the full motion range of the device is within the measurement range and the laser is parallel to the extension direction.
3. Start recording the pressure and displacement data with LabVIEW (4K samples at 500Hz)
4. Using the input syringe, slowly drive water into the device until it is fully extended
5. Once fully extended, allow the compression spring within the device to fully retract the device

The hydraulic line pressure and device extension data are shown in Figure 5.10. From the plots, the pressure to initiate motion and to fully extend the device were determined be to approximately 175 kPa and 285 kPa, respectively. The reason the pressure to fully extend was greater than the pressure to initiate motion was because as the device is extended, the spring within the housings becomes more compressed. Thus, as the device is extended, the required pressure increases. Despite exceeding the operating pressures by reaching 375 kPa, no device leaking was observed. These results successfully proved the performance of the device on the benchtop, supporting further validation *in vivo*.

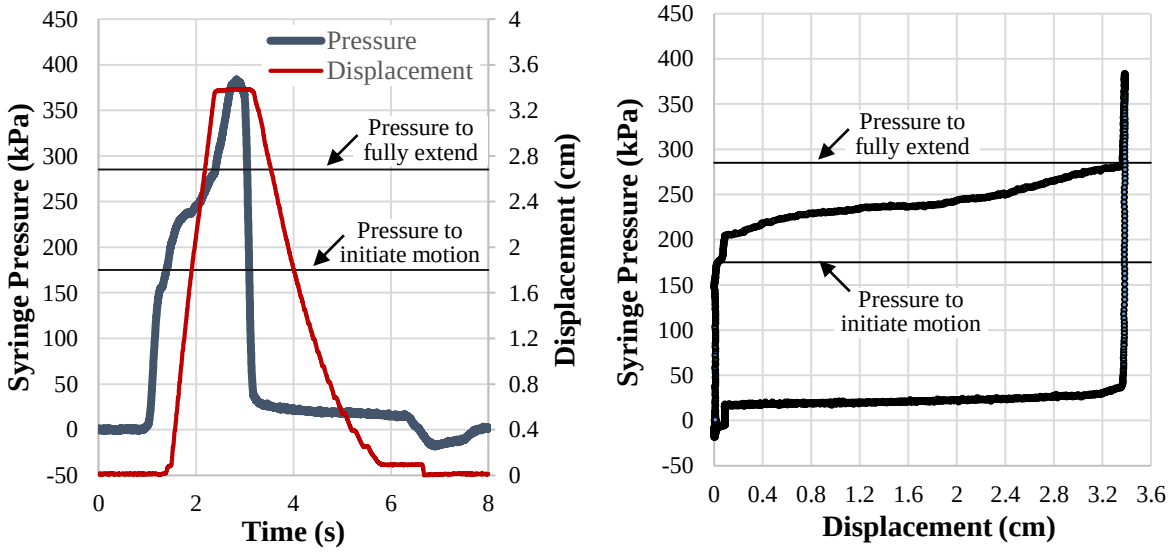


Figure 5.10. Benchtop Characterization of Reciprocating Linear Hydraulic Device.
The input syringe pressure and device displacement data are plotted against time and each other. The data show the pressure required to initiate the motion of the stage, 175 kPa, the pressure to fully extend the stage, 185 kPa, and the total expansion of the device, 3.4 cm.

5.3. *In Vivo* Experimental Growth Study

To validate the operation of the Reciprocating Linear Hydraulic Device *in vivo*, and more importantly, to demonstrate that the payout approach to growing small bowel is achievable, an *in vivo* study was conducted with a porcine animal model. The ultimate goal of the experiment was to increase a length of bowel by an amount that is greater than the stroke of the device, because this would establish that the payout approach is feasible. In the following section, the experimental procedure and results are discussed.

5.3.1. *In Vivo* Experiment Procedure

The procedures of the *in vivo* experiment consist of the procedure for the surgical implantation of the device, the device expansion procedure, and the tissue analysis and growth measurement plan. Although the surgical implantation of the Reciprocating Linear Hydraulic Device is almost identical to that of the Curved Hydraulic Device and the Instrumented SMA Driven Ratchet, the compact design of the device and the controlled intraluminal attachments enable less invasive implantation approaches. For example, the device could potentially be placed into the continuous GI tract through a gastrostomy and guided into the small bowel with an endoscope placed through the upper GI tract. More optimally, with some refinement the device could potentially be placed

through the upper GI tract and require little to no surgical tissue manipulation of the small bowel. All animal experiments were conducted at the University of Michigan with approval from the University Committee on the Use and Care of Animals (protocol number 09026).

5.3.1.1. Surgical Implantation Procedure

As shown in Figure 5.11, the Reciprocating Linear Hydraulic Device was implanted into a Roux limb rather than placed in the continuous GI tract. The procedure for the creation of the Roux limb matches that of the *in vivo* experiments described in Chapters Two and Three. In contrast to those *in vivo* experiments, the Reciprocating Linear Hydraulic Device was not fixed relative to the Roux limb by sutures and was free to slide through the bowel lumen when the attachments were disengaged.

The surgery began with a 15 cm midline incision to open the abdominal cavity of the porcine model. The small bowel was manipulated to determine the flow direction of enteral contents and to locate the Ligament of Treitz, which marks the start of the small intestine. Approximately 60 cm along the length of small bowel from the Ligament of Treitz, the small bowel was cut, creating two open ends of bowel labeled (a) and (b), as shown in Figure 5.11. Approximately 60 to 75 cm along the length of bowel from (b), an end-to-side anastomosis was created, connecting (a) to (c) and restoring the continuity of the GI tract. The segment of small bowel from (b) to (c), or Roux limb, was no longer in the continuity of the GI tract and would not pass ingested contents, however, the health of the Roux limb was maintained by the blood supply from the intact mesentery. During the creation of the Roux limb, the Reciprocating Linear Hydraulic Device was sterilized by soaking it in a liquid sterilant (Metrix, Metricide®) for the manufacturer recommend time of 40 minutes. After sterilization, the device was thoroughly rinsed with sterile saline to prevent any sterilant from getting into the surgical field, with special care was taken to completely remove sterilant from the mesh material of the attachments. The Reciprocating Linear Hydraulic Device was inserted, compliant tissue guide first, into the open end of the Roux limb. A stoma, or surgically created opening, was made in the skin and fascia of the abdomen, and the Roux limb was secured to the stoma at the fascia and skin. The final steps of the surgery were to route the hydraulic and pneumatic lines through the Roux limb, connect the external syringes to the lines, and secure the external syringes and control lines to the center of the porcine model's back. At the conclusion of

the implantation, the Roux limb was 70 cm in length and the device was implanted approximately 25 cm from the stoma.

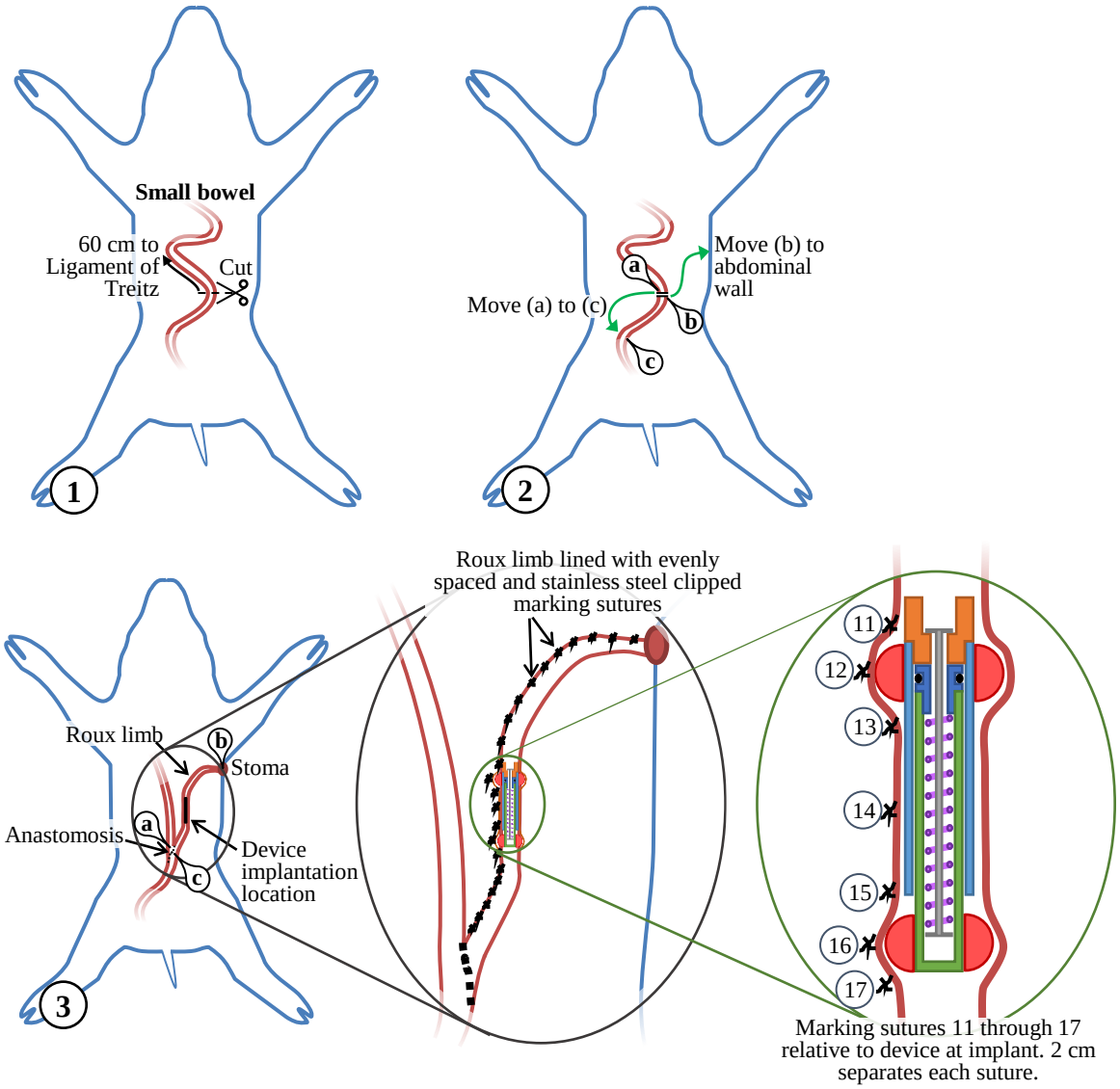


Figure 5.11. Surgical Implantation Procedure.
The device was implanted in a Roux Limb, removing it from the continuity of the GI tract and preventing bowel obstruction. The hydraulic and pneumatic lines were placed through the stoma and bundled on the back of the porcine model. To measure growth, evenly spaced marking sutures are placed along the Roux Limb and paired with radiopaque stainless steel clips. At explant, the distance between the sutures and the position of the sutures relative to the device were used to evaluate the tissue growth. At the time of the implant, sutures 11 (numbered from the stoma) through 17 were positioned along the device as shown. In total, 35 marking suture were placed along a 70 cm Roux Limb at implant.

5.3.1.2. Device Expansion Procedure

During the day of the operation, no extension of the device or inflation of the attachments was completed to allow the animal to rest. For the next six days post operation, the five-stage operation illustrated by Figure 5.4 was repeated four times per day, at 8 am, 12 pm, 4 pm, and 8 pm. At 8 am each post-operative day, the device was already contracted and the attachments are disengaged from the prior day. First, both attachments were engaged by inflating the distal and proximal balloons with approximately 15 mL of air. Then, the device was extended 3.4 cm by the injection of 2 mL of water into the hydraulic line, putting the bowel segment between the attachments under tension. Over the following four hours, the bowel tension decreased due to some combination tissue growth, tissue slipping, and/or viscoelastic effects until the next device expansion at 12 pm. At both 12 pm and 4 pm, the payout operation was continued by disengaging both attachments (deflating the balloons), retracting the device (drawing 2 mL out of the hydraulic line), reengaging both attachments, and extending the device. Finally, at 8 pm each day, the attachments were disengaged and the device was retracted, allowing the bowel to rest for 12 hours. The device was removed on the 7^{th} post-operative day during the explant surgery.

5.3.1.3. Tissue Measurement Plan

The net growth of the bowel in the Roux limb was evaluated using marking sutures onto which radiopaque stainless steel clips were attached. At the implant surgery, thirty five marking sutures were evenly placed along the entire length of the Roux Limb and three sutures (placed 2 cm apart) were placed on the normal fed bowel distal to the anastomosis. Initially, the markers on the Roux limb were also placed 2 cm apart. This marking approach was taken, because even if the implanted device changes position along the Roux Limb, measurements of the distance between the sutures at the explant can be used to estimate the net growth of the tissue. Figure 5.11 shows the 11th through the 17th (numbered from the stoma to the anastomosis) suture as they were aligned with the device at the implant.

5.3.1.4. *In Vivo* Performance of Device Validation Procedure

The performance of the Reciprocating Linear Hydraulic Device was evaluated once during each post-operative day to determine the presence of leaks in the hydraulic line or device housing, and leaks in the pneumatic lines and/or in either attachment. Because the device is inaccessible and not instrumented, the performance evaluation was in large part completed by comparing the

device usage experience to its performance in the laboratory. For example, from benchtop characterization, when there is not a "fast" leak, the pressure on the hydraulic line increases dramatically when the device was fully extended (Figure 5.10). Thus, this increase in pressure can be felt through the input syringe on the hydraulic line and suggests there is not a fast leak. The presence of a "slow" leak can be detected by a reduction of the water in the input syringe for the hydraulic line when the device is fully retracted. Similarly, to evaluate the presence of a fast leak in either attachment, the haptic feedback from the input syringe can be used. As the attachments are engaged, the pressure on the input syringe should increase as the syringe plunger drives more air into the attachments. The presence of a slow leak in either attachment can be detected by listening to the pneumatic lines when they are purposefully vented to atmospheric pressure, disengaging the attachments. If there was not a slow leak, the air held by the attachments (over 4 hours) made an audible sound as it rushed out of the pneumatic line.

5.3.2. *In Vivo* Experiment Results

The results of the *in vivo* experimental study include a description of the Reciprocating Linear Hydraulic Device performance, the measurement of the small bowel lengthening achieved by the payout approach, and an evaluation of the grown tissue health compared to controls.

5.3.2.1. Performance of Reciprocating Linear Hydraulic Device

The successful performance of the Reciprocating Linear Hydraulic Device depended on the lack of hydraulic (expansion mechanism) and pneumatic (attachments) leaks. Using the aforementioned method for detecting slow and fast leaks while the device was implanted, no fast leaks were detected in either the pneumatic or hydraulic lines, and no slow leak was detected for either attachment. A slow leak of approximately 0.1 mL/day was found in the hydraulic line, which was easily remedied by removing and refilling the syringe. Despite the slow leak in the hydraulic line, the overall performance of the Reciprocating Linear Hydraulic Device was excellent. At the explant, no damage to the device or corrosion was observed, supporting the use of 316 stainless steel and Delrin materials for device fabrication.

5.3.2.2. Tissue Growth Analysis

The extent of macroscopic tissue growth can be estimated by comparing the tissue marking suture measurements from the explant relative to the implant. Figure 5.12 shows the placement of

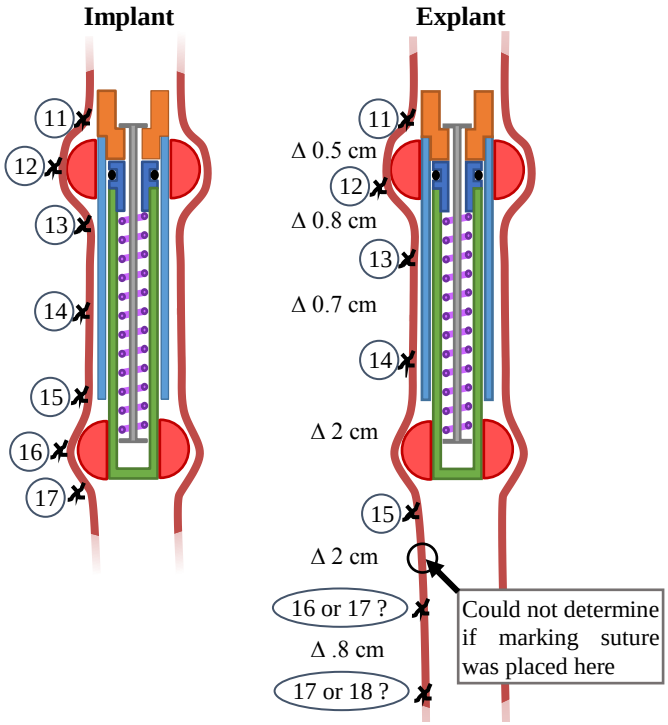


Figure 5.12. Growth Measurement.
The growth of the tissue was evaluated using marking sutures placed in the Roux Limb during the implantation by summing the change in the distance between adjacent markers. Based on the markers, the change in tissue length was 4 cm (worst case) to 6.8 cm (best case). The exact determination of the growth could not be made conclusively because it was unclear if a marker was missing at the explant distal to the 15th marker. If the marker was not missing, then the tissue grew 6.8 cm, which is twice the stroke of the Reciprocating Linear Hydraulic Device. If the marker was missing, the growth represent 120% of the device stroke, which still strongly suggests that the payout approach worked.

the device relative to the sutures at the implant and the explant, and the change in marker spacing between the markers that were originally on the device. Initially, the sutures were placed 2 cm apart, making the distance from the 11th to the 17th marking suture 12 cm. At the explant, the total tissue length from the 11th to the 17th marking suture was 16 cm to 18.8 cm, depending on whether a marking suture slipped out of the tissue distal to the 15th marking suture. Unfortunately, it was not possibly to determine whether this particular suture slipped out of the tissue or not during the distraction period with any certainty. Best case scenario, the tissue grew approximately 6.8 cm, which is twice the stroke of the Reciprocating Linear Hydraulic Device. In this case, lengthening the tissue by twice the stroke of the device very strongly demonstrates that the payout approach to tissue lengthening is feasible. In the worst case scenario, the tissue grew 4 cm, which is 120% of

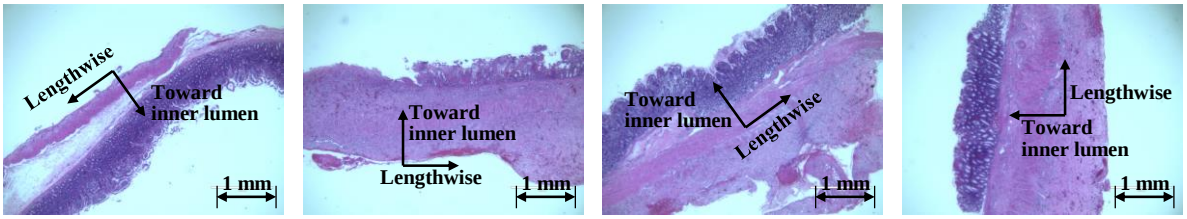
the device stroke and still suggests that the payout approach is feasible. In either case, there are some definitive results that can be made from tracking the known marking sutures. First, the tissue segment from suture 11 to suture 15 expanded from 8 cm at implant, to 12 cm at explant, growing by 50%. And second, the tissue marked by sutures 16 and 17 was successfully paid out from the device. These two definitive results strongly suggest that the attachments were able to both apply bowel tension and slide through the bowel lumen, and of equal importance, that the payout approach to bowel lengthening is feasible.

5.3.2.3. Grown Tissue Health

To determine if true small bowel growth occurred rather than permanent deformation, the tissue health of the grown small bowel segment was compared to the health of control samples taken from the Roux limb and to tissue samples taken from normal small bowel. To evaluate tissue health, the tissue histology was observed for microscopic damage, and the morphology and rate of cell proliferation were measured. Although there was superficial mucosal disruption observed in the tissue samples taken from the distal and proximal tissue attachment sites, the result of the evaluations suggested that true growth of the small bowel was successfully induced.

5.3.2.3.1. Histology

Histologic slides of tissue samples from the Roux limb control, the site of the distal attachment, the middle of the device, and the site of the proximal attachment are shown in Figure 5.13. The key result from the histologic evaluation of tissue health was that the attachment sites showed significant epithelial sloughing and general disruption of the mucosal layer without damage to the underlying submucosa and muscle layers. In contrast, histology of the grown tissue between the attachments was atraumatic. Although not preferred, the damage to the mucosal layer



a). Roux Control **b). Distal Attachment** **c). Mid Device** **d). Proximal Attachment**

Figure 5.13. Tissue Histology.
The tissue histology from the Roux limb control, the site of the distal and proximal attachments, and the middle of the device show at that the attachment sites, there is significant epithelial sloughing without damage to the submucosa or muscles layers, while the tissue growth in between the attachments was atraumatic.

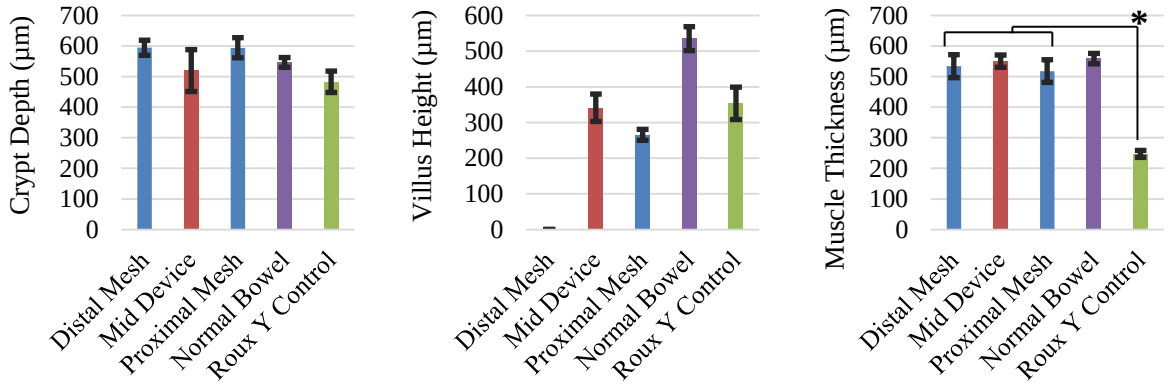


Figure 5.14. Tissue Morphology.

Morphologic measurements of the crypt depth, villus height, and muscle layer thickness show that while the crypt depth and villus height were preserved relative to the Roux limb control, the muscle layer thickness was greatly increased. Villi could not be identified at the site of the distal mesh. Pairwise t-Tests were taken for the distal mesh against the Roux Y control, the proximal mesh against the Roux Y control, and the mid device against the Roux Y control. *Brackets indicate statistically significant differences ($p < 0.05$).

at the attachment sites is clinically acceptable because in the absence of the attachments, the mucosal layer will heal.

5.3.2.3.2. Morphology

Morphologic measurements of the crypt depth, villus height, and muscle layer thickness are shown in Figure 5.14. Compared to the Roux limb, the crypt depth of tissue samples taken from the distal attachment site, proximal attachment site, and the middle of the device were preserved. The villus height was also not statistically significant from the Roux limb for the middle of the device and the proximal attachment site. Villi could not be identified in the sample taken at the distal attachment site due to mucosal disruption. Consistent with the bowel growth achieved in Chapter Two, Chapter Three, and prior research [4–6,10,12], the muscle layer thickness of the grown tissue was much greater than that of the Roux limb control.

5.3.2.3.3. Cell Proliferation

Measurements of epithelial cell proliferation in tissue samples taken from the distal attachment, proximal attachment, the middle of the device, the Roux limb control, and normal bowel are shown in Figure 5.15. Compared to the Roux limb control, an increase in cell proliferation was measured for tissue samples taken from the middle of the device and the distal and proximal attachment sites. Although the increase in cell proliferation measured for the tissue

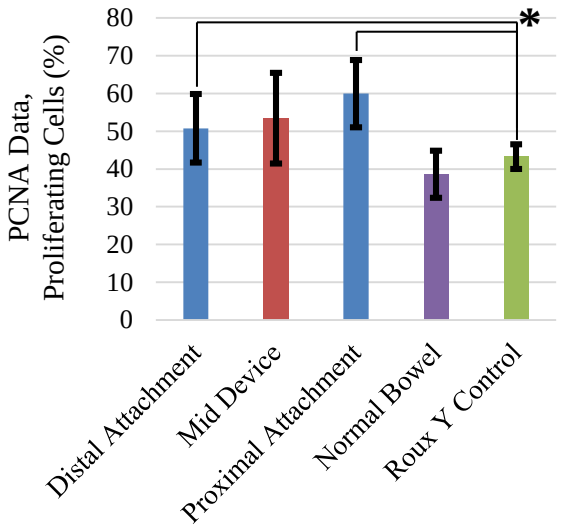


Figure 5.15. Cell Proliferation.

The measurements of cell proliferation in the tissue samples taken at the attachment sites, the middle of the device, normal bowel, and the Roux limb control show that the attachment sites had statistically greater cell proliferation than the Roux limb control. Pairwise t-Tests were taken for the distal mesh against the Roux Y control, the proximal mesh against the Roux Y control, and the mid device against the Roux Y control. *Brackets indicate statistically significant differences ($p < 0.05$).

taken from the middle of the device was not statistically significant. This results suggested that true bowel growth was occurring and indicated the health of the mucosa.

5.4. Conclusion

Short bowel syndrome remains a difficult condition to manage and treat, leading to high mortality rates. To research a novel treatment of SBS based on inducing the growth of remnant small bowel tissue with tensile loading, many enterogenesis devices have been developed to study mechanotransductive enterogenesis in rabbits, rats, and pigs. However, these devices were designed with a focus on research and were not extendable for clinical applications due to limitations in their implantability, device form, tissue lengthening capacity, and lack of force instrumentation. To improve the state of the art, this chapter developed the Reciprocating Linear Hydraulic Device, a compact enterogenesis device technology with the potential to enable minimally invasive surgical implantation and removal, and high-expansion tissue lengthening not limited by the stroke of the device.

The focus of the design was on the expansion mechanism of the enterogenesis device, because a promising and clinically relevant attachment approach was identified in Chapter 4. To

comprehensively explore the design space of enterogenesis device expansion mechanisms, seven distinct approaches were conceptualized. Among the expansion approaches, a novel tissue lengthening approach based on paying out small bowel tissue was selected. The defining advantage of the payout approach for bowel lengthening is that the net growth of small bowel is not limited by the device stroke, which is constrained by the peritoneal cavity of patients, or by the length of the patient's remnant bowel.

The Reciprocating Linear Hydraulic Device was designed and fabricated to evaluate the feasibility of the payout approach to bowel lengthening, and to demonstrate a scalable compact expansion mechanism with clinical applicability. A one week *in vivo* experiment with a porcine animal model was conducted with the goal of growing a length of bowel greater than the device stroke of 3.4 cm while maintaining the health of the tissue, thereby demonstrating the feasibility of the payout approach. Difficulty recovering the marking sutures at the explant surgery made the measurement of net bowel growth difficult, but the tissue lengthened by 4 cm in the worst case, and 6.8 cm in the best. To health of the tissue was examined by observing the tissue histology, and measuring the tissue morphology and cell proliferation. Although the mucosal layer of the tissue was disrupted at the attachment sites, the mucosa would regenerate in the absence of the attachments and there was no damage in any other areas of the sampled tissue. The medical evaluation of the tissue suggested that true growth of the small bowel was achieved. Whether the tissue lengthened by 4 cm or 6.8 cm, the feasibility of the payout approach and performance of the Reciprocating Linear Hydraulic Device were successfully demonstrated.

The viability of the payout approach has a large impact on the design of enterogenesis devices, because the ability to grow a segment of remnant bowel multiple times in the same implantation period enables the design of compact enterogenesis devices with the ability to induce large net bowel growth. Regardless of the linear expansion actuator architecture, there is a tradeoff between actuator length and actuator stroke. This fundamental tradeoff makes the design of a compact enterogenesis device capable of producing large net bowel growth difficult. However, the strength of the new payout approach is that it makes this tradeoff irrelevant. The clinical implication of enabling compact enterogenesis devices is that they permit non-invasive surgical techniques for device implantation and removal into continuous bowel, resulting in faster recovery, reduced cost of treatment, less (if any) scarring, reduced complication risk, shorter hospitalization, and an overall better quality of patient care.

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CHAPTER SIX. CONCLUSION

The ultimate purpose of this body of research is to hasten the realization of the mechanotransduction approach for correcting short bowel syndrome such that it becomes a real clinical alternative to bowel restructuring surgeries and transplants. This dissertation has made very significant contributions towards this vision, both from a medical and from a technological standpoint.

This chapter presents a restatement of the research goal and objectives, summarizes the research, and discusses the findings and contributions of this dissertation, which are organized into four themes: medical treatment, device innovation, experimental methodologies, and mechanical device/tissue interface. The impact of these contributions are discussed, and the chapter closes with future research recommendations to guide the direction of this continuing research effort.

6.1. Goal and Objectives

The goal of this research was to explore technological approaches for a promising and novel treatment method of short bowel syndrome based on mechanotransduction. Four key research objectives have been identified and accomplished toward to the achievement of this goal:

1. **Treatment Approach Feasibility and Potential.**
   Investigate the potential for inducing large net growth, large expansion factor growth, and inspect the mesentery for an increase in the vascularity to evaluate the feasibility of mechanotransduction for correcting short bowel syndrome and to support further research into the technologies for and the development of mechanotransduction-based treatment approaches.

2. **Treatment Development**
   Create technologies and perform studies to determine the upper bound of safely applied bowel tension, compare the effect of applying different tissue expansion profiles on tissue growth, and explore the limits of the maximum small bowel expansion rate to develop the best practices and methods for safely and effectively exploiting mechanotransduction.

3. **Tissue Attachment**
   Develop clinically relevant tissue attachments for the safe attachment and detachment of an expansion mechanism to the small bowel. Identify the risk of surgical complications associated with a range of attachment approaches, including perforation and ischemia, and measure their attachment and detachment performance.

4. **Clinically Relevant Device**
   Develop and demonstrate a clinically relevant enterogenesis device and treatment method for pediatric and adult SBS by demonstrating very high net bowel growth. The *in vivo* validation of the device with porcine models must produce medical results for promoting clinical trials by achieving high expansion factor growth backed by analysis of the tissue to demonstrate its health and functionality.

6.2. Research Summary

The process of developing the mechanotransduction-based treatment approach was highly multidisciplinary, requiring contributions from both medical and engineering research to be successful. Medical challenges included demonstrating the feasibility of the approach in clinically relevant animal models and identifying methods of efficiently and safely exploiting mechanotransductive growth. Addressing these medical challenges required the development of novel enterogenesis devices designed for clinically relevant animal models with new capabilities that were not available in the previously limited state of the art.

To achieve the first objective in Chapter Two, the feasibility of growing small bowel in clinically relevant porcine models was established in a series of *in vivo* medical experiments supported by the design and fabrication of the Curved Hydraulic Device, an enterogenesis device capable of doubling the length of the small bowel segment in which it is implanted. The design considerations for the device were related to the device form, sealing, and the mechanical device/tissue interaction. The Curved Hydraulic Device was fabricated by traditional milling operations from biocompatible Stainless Steel and Delrin materials. To give the device its

curvilinear form factor, the stainless steel housing and stages were manually curved around a circular mandrel. A benchtop experimental characterization of the device expansion versus input working fluid volume was completed, allowing the displacement of the stages to be estimated while the device was implanted. Four *in vivo* experiments were conducted where the expansion of the small bowel tissue ranged from 1.6 to 2.2X. To support the conclusion that true growth was occurring rather than permanent tissue deformation, tissue samples were taken and compared with relevant controls to evaluate tissue morphology, cell proliferation, barrier function, and to observe the adaptation of the vasculature in the supporting mesentery. The results of these experiments have successfully established the feasibility of growing small bowel in clinically relevant animal models through the demonstration of significant small bowel growth, mesenteric angiogenesis, and the examination of tissue morphology, cell proliferation, and barrier function.

To achieve the second objective, Chapter Three expanded on these results by exploring methods of efficiently exploiting the growth process through the comparison of tissue expansion strategies and by determining the maximum safely applied small bowel tension. These medical studies required an enterogenesis device with displacement control and real-time tracking of the applied bowel tension and displacement. To enable these studies, a force and displacement instrumented SMA driven ratcheting device was developed. A scalable SMA driven ratcheting mechanism design methodology was developed, validated, and successfully applied to the enterogenesis device design. *In vivo* experimental studies with porcine animal models using the Instrumented SMA Driven Ratchet suggested that small bowel growth can be induced much more rapidly than previously attempted by using a load-based tissue expansion strategy, the tissue responds to low magnitudes of force, and that bowel may grow more readily as the implantation and device expansion progresses. Additionally, the Instrumented SMA Driven Ratchet was used in acute *in vivo* experiments to determine the maximum safely applied small bowel tension in porcine models. As with the feasibility studies in Chapter Two, the health and functionality of the grown tissues segments were compared to relevant controls, demonstrating true growth.

To achieve the third objective, Chapters Four explored the design of clinically applicable device-to-tissue attachments to overcome the challenge of safely and reliably attaching to and detaching (for implantation, removal, and repositioning) small bowel. Prior research attachment approaches included end-abutment and sutured attachments, but neither approach is clinically

relevant because they preclude minimally invasive device implantation and removal. Sutures are not reliable for tensioning soft tissue – the enterogenesis study using sutured attachments reported that the sutures slipped through the rabbit small bowel [1], sutures slipped through small bowel tissue in all of the *in vivo* studies with the Curved Hydraulic Device that exceeded 2 weeks, and this complication has been reported in the treatment of long-gap esophageal atresia [2,3], where esophageal tissue is tensioned by sutures. The end-abutment approach requires the grown bowel tissue to be isolated from the GI tract and the use of several anastomoses, which lead to the need to discard small bowel tissue when the grown segment is placed back into the continuity of the GI tract. To provide a clinically relevant attachment, many approaches for attaching to and detaching from the small bowel were evaluated in *ex vivo* and *in vivo* experiments. Several qualitative trade-offs were found. Attachments that gripped the bowel well also posed the greatest tissue health concerns, such as bowel perforation and ischemia. Furthermore, attachments that gripped the bowel well did not also detach well from the tissue, making their implantation difficult and/or unsafe. The conclusion of the chapter compared all of the evaluated attachment approaches and recommended a promising and clinically relevant attachment approach, the Dilating Fenestrated Mesh.

To achieve the fourth objective, Chapter Five presented the development of an enterogenesis device designed with a focus on clinical relevance over research applicability. Specifically, the chapter focused on the design of the expansion mechanism, which integrated with the attachments recommended in Chapter Four to create a clinically relevant enterogenesis device with significant advantages compared to the current state of the art. Compared to the research-focused devices of Chapters Two and Three, there were greater design constraints for a clinically relevant device. The most important differences were the need to be able to implant the device in a continuous segment of the small bowel (by non-invasive surgical techniques) rather than within an isolated segment, greater constraints on the form of the device, greater lengthening capabilities to enable the treatment of severe cases of SBS, and an enhanced emphasis on device safety features including applied tensile load measurement, displacement control, and displacement measurement. To develop the clinically relevant enterogenesis device, a design process was conducted from the earliest stage of requesting customer requirements to the later stage of evaluating the *in situ* performance of the device. Seven distinct conceptual approaches to lengthening small bowel tissue

were identified, from which the novel payout approach was selected. The payout approach is a high-fold bowel tissue growth approach based on applying tension, allowing time for the bowel to respond by growing, reestablishing the implanted condition of the device, and repeating. An embodiment of the payout approach, the Reciprocating Linear Hydraulic Device, was fabricated and characterized on the benchtop. Using the device, a one-week *in vivo* experiment with a porcine animal model was conducted to validate the performance of the device and demonstrate the viability of the payout approach. The results of the experiment supported the viability of the payout approach, because the net bowel lengthening exceeded the device stroke and the health of the tissue was largely maintained.

6.3. Medical Treatment Contributions

Critical contributions in the development of the mechanotransduction-based treatment for correcting short bowel syndrome have been made in this dissertation. Most importantly, this dissertation has established the feasibility of the treatment approach in clinically relevant porcine animal models. Additionally, studies comparing tissue expansion strategies based on tissue displacement rates or/and the applied tensile load were conducted with the Instrumented SMA Driven Ratchet. These studies showed that basing the expansion of bowel tissue on the applied tensile load results in much higher rates of expansion (without affecting the tissue health) than setting a fixed tissue displacement rate. Lastly, the medical viability of tensioning and relaxing the same segment of bowel tissue multiple times to induce high fold growth was demonstrated, supporting the design of ultra-compact enterogenesis devices that can enable non-invasive surgical techniques.

6.3.1. Feasibility of Mechanotransduction Approach

Although load induced small bowel growth was previously demonstrated in rabbit and rat models, the clinical relevance of these studies was limited by the use of small animal models. By inducing the longitudinal growth of porcine small bowel, comparing the health of the grown segments to appropriate controls, and measuring the vascular adaption of the mesentery supporting the growth segment [4], the clinical feasibility of the treatment approach was established.

The feasibility of an alternate treatment approach is huge, because current treatments for short bowel syndrome are associated with potentially lethal complications, leading to high mortality

rates. Furthermore, the impact of this result is not limited to just patients suffering from short bowel syndrome, because the method has the potential to become an alternative to bowel transplants for a broader range of indications. In the context of this dissertation, the demonstrated clinical feasibility of the treatment approach has provided the motivation and the foundation from which to further develop technologies for treating short bowel syndrome by inducing bowel growth through mechanotransduction.

6.3.2. Profile Comparison

The expansion of an enterogenesis device can follow a number a strategies based on a maintaining a tissue displacement rate, a constant tensile tissue load, or a mixed piecewise displacement and load based approach. The effect of these three approaches on the growth rate and health of small bowel tissue was investigated in a series of *in vivo* experiments with the Instrumented SMA Driven Ratchet. An important conclusion of this series of experiments was that expanding the tissue based on real-time measurements of the applied tension enabled much higher rates of growth compared to displacement rate based expansion strategies without negatively affecting tissue health.

Without applied tissue tension feedback, the tissue expansion rate must be conservatively set to prevent complications related to exceeding the maximum safe tension. In prior experiments using the Curved Hydraulic Device, the strain rate of the tissue was set to less than 10% (of the starting segment length) per day. By using the applied tissue tension feedback to inform the tissue expansion, the rate of bowel tissue growth achieved was approximately 3.5 fold more rapid, without approaching unsafe magnitudes of applied tension, than expansion rates used in prior experiments with un-instrumented devices.

This result is important for several reasons. From a practical standpoint, increasing the rate of bowel growth such that the implantation period lasts less than 30 days will lessen restrictions from the FDA (Investigational Device Exemptions, 21CFR812.3). In a clinical setting, increasing the rate of bowel growth will lead to lowered costs of care, reduced risk of complications, reduced patient discomfort, and a more rapid transition from parenteral nutrition to a normal oral diet.

6.3.3. Payout Approach

Most research devices for studying mechanotransductive enterogenesis, including the Curved Hydraulic Device and the Instrumented SMA Driven Ratchet, have used the *extension* approach to inducing tissue growth. Although these devices have been essential for research, all extension-based devices have one disadvantage in common: the net amount of tissue lengthening is limited to the stroke of the expansion mechanism and thus the size of the patient's peritoneal cavity and/or remnant bowel length. Devices based on the novel payout approach to tissue lengthening do not have this disadvantage, because payout devices, upon inducing one device stroke's amount of bowel growth, can detach from the bowel wall, reset/retract, reattach, and repeat the operation *ad infinitum* to induce large net tissue growth with a compact device.

The potential for this bowel lengthening approach to be used for correcting short bowel syndrome is large, because the net increase in bowel length would not be limited by the length of the device, the length of the patient's remnant bowel, or the space within the peritoneal cavity. However, until recently, the approach had never been considered or experimentally demonstrated. Using an embodiment of the payout concept, the Reciprocating Linear Hydraulic Device, the growth of small tissue by 120% to 200% of the device stroke was induced using the payout operation, demonstrating its viability.

The successful demonstration of the payout approach has a great impact on the design of enterogenesis devices for treating SBS. The main impact is that enterogenesis devices can be designed more compactly because the bowel growth will not be limited to the device stroke, which is strongly coupled to the device length regardless of extension mechanism architecture. A more compact device is less likely to cause complications such as bowel obstruction, bowel perforation, and mesenteric tearing. Additionally, compact devices will enable less invasive surgical implantation and removal surgeries, resulting in faster recovery, reduced cost of treatment, less (if any) scarring, reduced complications, shortened hospitalization, and an overall better quality of patient care.

6.4. Device Innovation Contributions

The medical treatment contributions were made by conducting *in vivo* experiments that were enabled for the first time by the development of a series of novel enterogenesis device technologies

designed for porcine animal models. In addition to supporting the clinically relevant research studies presented in this dissertation and facilitating future studies of mechanotransductive enterogenesis, these novel technologies and the design methodologies used to create them represent a large step forward in the development of innovative enterogenesis device technologies for correcting short bowel syndrome.

6.4.1. Novel Technologies

Three actuation architectures with unique features and functionality have been developed to enable studies of mechanotransductive growth with porcine animal models, the Curved Hydraulic Device, the Instrumented SMA Driven Ratchet, and the Reciprocating Linear Hydraulic Device. Each device was designed to demonstrate and give insight on a specific aspect of mechanotransductive enterogenesis in porcine animal models, including clinically feasibility, methods of efficiently and safely inducing small bowel growth, and the viability of the payout approach to high-fold tissue lengthening. Additionally, all devices provided robust expansion platforms for evaluating a broad range of small bowel tissue attachment approaches.

6.4.1.1. Curved Hydraulic Device

The telescoping Curved Hydraulic Device is a novel hydraulic device architecture designed for enterogenesis studies of treatment approach feasibility with porcine animal models. For enterogenesis studies, the Curved Hydraulic Device had two important advantages compared a linear hydraulic architecture. First, the curvilinear form factor was better suited for the naturally forming curves of the small bowel and eliminated extraneous mesenteric tension, preventing mesenteric tears and secondary complications. Second, within the space-constrained peritoneal cavity, the curvilinear form factor increased the capacity for net bowel growth, because a curved path between the two attachments is greater in length than the corresponding linear path. The Curved Hydraulic Device enabled studies of treatment feasibility by having the capability to lengthen small bowel tissue by a large net amount (15 cm) and large expansion ratio (2X and greater, depending on initial attachment placement). Lastly, the Curved Hydraulic Device architecture can be potentially scaled for a broad range of actuation needs for applications such as powered joint prosthetics/orthotics, automotive applications, and robotic actuators.

6.4.1.2. Instrumented SMA Driven Ratchet

The ratcheting mechanism is a compact external architecture for accumulating the small displacements of SMA wire with important SMA actuator features such as the integrated adjustable martensite hard stop and the vented-screw SMA wire mounts, which enabled the SMA tension to be adjusted after installation. Ratcheting mechanisms are an important external architecture for SMA wire actuators, because they overcome one of the major disadvantages of the actuator, its low actuation strain, which is typically limited to 2 to 8%. Unlike other internal or external SMA architectures for increasing stroke, like the SMA helix [5] or web architectures [6], linear ratcheting mechanisms do not tradeoff force with stroke. Additionally, SMA driven ratcheting mechanisms are advantageous because they have repeatable displacement, zero-power hold, and because SMA is a lightweight, compact, and energy dense actuator, SMA driven ratcheting mechanisms are lighter and more compact than their traditionally actuated countertypes. Given its compact size and scalable design models, the SMA driven ratcheting mechanism can be used in a wide variety of ratcheting applications where high actuation frequency is not required.

6.4.1.3. Reciprocating Linear Hydraulic Device

The Reciprocating Linear Hydraulic Device is a unique compact hydraulic device due to its ability to retract without requiring separate extension and retraction lines. Instead, the device retracts from the force provided by an internal compression spring, making the design more compact by eliminating one seal and one hydraulic line compared to tradition hydraulic actuators. The compact size and retractability of the Reciprocating Linear Hydraulic Device made it an ideal platform for evaluating attachments and demonstrating the payout approach in live porcine animal models. In concert with the Dilating Fenestrated Mesh Attachment approach, the integrated Reciprocating Linear Hydraulic Device represents a leap forward in the capabilities of enterogenesis device technology for correcting SBS by enabling minimally invasive surgical device implantation and removal, in continuity device placement, and high-fold bowel growth not limited by the stroke of the device.

6.4.2. Design Methodologies

To design the Instrumented SMA Driven Ratchet, the Reset View Design Methodology and an analytical model of the ratchet rack and pawl force interaction were developed. Although

created for the design of a compact SMA driven ratcheting mechanism, the Reset View Design Methodology is a general graphical approach for designing SMA actuators biased by a reset element that greatly facilitates the selection of the reset element. Similarly, the analytical ratchet rack and pawl force interaction model is scalable, making the model useful for designing a large range of actuated linear ratcheting mechanisms.

6.4.2.1. Reset View Design Methodology

Although used to in this dissertation to design the Shape Memory Alloy (SMA) driven ratcheting mechanism, the Reset View Design Methodology is a general approach for designing any SMA actuator with a bias element to re-strain the SMA wire between actuations. SMA wire is linear actuator composed of nickel and titanium that contracts as it transitions from its martensite phase (cool) to its austenite phase (hot). Without external tension, SMA wire does not typically re-lengthen as it transitions in the other direction, from austenite to martensite. Thus, the actuator is often coupled with a reset spring or bias element to serve this purpose. Compared to the traditional graphical design approach for SMA actuators, the Reset View Design Methodology is particularly useful for designing SMA actuators where a constraint on the length of the SMA wire is enforced, because the method readily illustrates the impact of spring selection on SMA stroke.

The successful realization of any SMA actuated device is contingent on the coupled design of the SMA design parameters (diameter, length) and reset spring parameters (stiffness, maximum suggested load/deflection, solid height, etc). However, the design space of springs is far richer than that of SMA wires, which is limited to a handful of commercially available wire diameters. Because of this, a design method where the reset spring is specified *after* the selection of an SMA wire is more intuitive than first specifying the reset spring and then selecting an appropriate SMA wire diameter. The Reset View Design Methodology is powerful because it enables this approach, resulting in more robust SMA actuated device designs regardless of actuator scale or application field.

6.4.2.2. Ratcheting Rack-Pawl Force Interaction Model

Although SMA wire is an energy dense, lightweight, and compact actuator capable of providing moderate forces, the material has limited actuation strains on the order of 2-4%. External architectures that can accumulate the displacement provided by the SMA wire, like a ratcheting

mechanism, greatly expand the application space of SMA. To better design SMA actuated linear ratcheting mechanisms, an analytical model of the ratcheting rack-pawl force interaction was developed and experimentally validated. The model predicts the force and displacement required by any linear actuator (not just SMA wire) to advance the position of the rack by its pitch. This predication was key to the design of the SMA actuator for the Instrumented SMA Driven Ratchet. However, because the model is scalable, it can be used to predict the forces and displacements required by much smaller or larger devices.

6.5. Experimental Methodology Contributions

While novel enterogenesis device technologies were critical for enabling the *in vivo* studies of mechanotransductive enterogenesis presented in this dissertation, the development and refinement of experimental methods was necessary to conduct the experiments and evaluate their results. In Chapter Three, the second objective of developing the treatment approach was achieved by determining the upper bound of safely applied bowel tension, comparing the effect of applying different tissue expansion profiles on tissue growth, and exploring the limits of the maximum expansion rate of the small bowel. A key device capability to enable these studies was the real-time measurement of bowel tension within live pigs. Thus, a method for isolating the measurement of the applied small bowel tension was needed. Across all trials, methodologies for evaluating the tissue growth and health were developed or refined to determine that the observed bowel lengthening was a result of growth rather than permanent tissue deformation.

6.5.1. Bowel Tension Measurement

The techniques for measuring the applied tensile load have significantly evolved over the course of this research. In the beginning, the measurement of the bowel tension was captured by placing a force sensor on the end of the device, which was only compatible with the end-abutting tissue attachment approach that is not extendable to clinical application. Additionally, this measurement architecture measured *all* external loads on the device, not just those due to the bowel tension. The sources of these loads were due to the position and activity level of the animal model, and were an order of magnitude higher than the bowel tension. Some measurement of the bowel tension is better than nothing, but the captured data was noisy, often saturated the data acquisition

electronics, and placed time-varying offsets on the measured load that could not be distinguished from the bowel tension.

Initially, to isolate the measurement on the contribution from the bowel tension, experiments were conducted where the segment of bowel with an early version of the Instrumented SMA Driven Ratchet was placed inside of an isolation tube. Although the measurement of load was considerably cleaner, this approach was not surgically favorable because of the large size of the isolation tube and the reaction of the adjacent tissues during the implantation period. The design of the isolation tube was challenging because it had to have a lengthwise slot for the mesentery. If the slot was too narrow, external loads on the isolation tube could cause the slot to pinch the mesentery. If the slot was too wide, loops of bowel could slide into the isolation tube during the experiments and become necrotic and/or obstructed. Also, to prevent the isolation tube from twisting and/or moving into an unfavorable position, it was sewn into the fascia of the peritoneal cavity through a series of holes opposite the slot. At explant surgeries, several surgical issues were observed where the isolation tube was used. The bowel tissue within tube grew into the holes, essentially anchoring itself and resisting lengthening. Worse, loops of bowel were observed inside of the isolation tube that were packed tightly enough to cause ischemia and necrosis. These surgical issues made it clear that the isolation tube approach should be abandoned, but the accurate measurement of the applied bowel load was still critical to enable important medical studies.

Thus, a key contribution of the Instrumented SMA Driven Ratchet was the force instrumentation system, whose mechanical architecture made the accurate measurement of the applied tensile load possible by greatly attenuating external loads on the device due to the activity and/or position of the porcine animal model. The external load attenuation was achieved by creating a rigid external load path around the force sensor. The real-time measurement of the applied bowel tension was critical for conducting the enterogenesis studies where the bowel tension was used to inform the tissue expansion procedure and for maintaining a safe range of loads on the small bowel during the distraction period. Additionally, the data acquisition rate and measurement sensitivity was able to capture peristaltic action, an important health indicator of bowel motility.

The clinical impact of this contribution is important, because the safe application of the mechanotransductive treatment approach will rely on not overstressing the remnant small bowel,

which could lead to ischemia and a cascade of worsening complications. Although a low bowel tension could be achieved by very conservatively expanding the remnant bowel, this approach is not in the best interest of patients because it lengthens the duration of the treatment, increases the risk of general complications related to the presence of a foreign body, and increases the cost of care. The measurement system can also be extended for research and clinical applications in other tubular tissues such as large blood vessels, the esophagus, and the colon.

6.5.2. Tissue Health and Growth Analyses

To support experimental studies, techniques for measuring the net growth of small bowel and quantifying the neovascularization of the mesentery supporting the bowel were developed. Additionally, an important finding regarding cell proliferation measurement techniques was made.

6.5.2.1. Tissue Length Measurement

To measure the net growth of small bowel in enterogenesis studies, a method based on the use of marking sutures was developed. For the method, evenly spaced sutures are placed along the Roux limb and along a segment of normal bowel to act as a control, and stainless steel clips are placed on every other, or every, suture. By remeasuring the marker spacing at explant, the small bowel growth can be recorded and compared to the control. This approach to measuring the change in bowel length is particularly advantageous for enterogenesis devices with non-permanent attachments (designed to actively attach and detach), because they may displace relative to the bowel. In contrast, for devices using permanent attachments (not designed to actively attach and detach) like sutures, the tissue length change was simply determined by measuring the displacement between the proximal and distal device-to-tissue attachments.

6.5.2.2. Measurement of Neovascularization

One important and previously overlooked aspect of healthy small bowel growth is the adaptation of the mesentery supporting the lengthened tissue. Compared to controls, the mesentery supporting the growth segments had increased neovascularization to support a greater demand for blood from the lengthened tissue. This result was important to establishing the feasibility of the mechanotransductive approach to correcting short bowel syndrome. To quantify this increase in neovascularization, several approaches were explored including immunofluorescence staining, using a laser Doppler system to measure blood perfusion, and the use of micro-CT scanning

technology to create 3D reconstructions of the blood vessels [4]. Among these methods, the use of micro-CT scanning technology was the most successful approach because it could be used for large (representative) areas of the mesentery.

6.5.2.3. Measurement of Cell Proliferation

Both bromodeoxyuridine (BrdU) and proliferating cell nuclear antigen (PCNA) staining techniques were used to identify proliferating cells in the mucosa of tissue samples taken from normal bowel, the unfed Roux limb, and from the distracted bowel segment. In studies where both approaches were taken, the results were in strong agreement. BrdU, however, is difficult to administer because it is designed for use with living tissue, and must be timed carefully to capture the proliferation of cells at a moment of interest. Furthermore, because it must be used with living tissue, its injection into the peritoneum must occur hours to days before the explant. To achieve this, a catheter placed during implant surgeries (which was flushed daily to prevent clogging) was used to inject BrdU. One important finding is that the use BrdU seemed to correlate with more severe adhesions at explant surgeries, one of the main reasons its use was discontinued during this research. In contrast, PCNA staining for cell proliferation is a routine lab procedure that provides results in strong agreement with BrdU without causing problems like strengthened intraperitoneal adhesions. Thus, PCNA was a more advantageous approach to measuring cell proliferation than BrdU.

6.6. Mechanical Device/Tissue Interaction Contributions

Across all *in vivo* experimental studies, regardless of the enterogenesis device, important contributions and findings were made regarding the mechanical device/tissue interaction. These findings and contributions include the determination of the maximum safely applied bowel tension, methods for attaching to bowel tissue, and important considerations for designing the form of enterogenesis devices.

6.6.1. Safe Load Determination

To safely use enterogenesis devices for research and clinical applications, the range of safely applied tensile loads was determined, and the dominant failure mode of the bowel tissue was identified. Based on *ex vivo* and *in vivo* experimental studies using segments of porcine small bowel, the risk of tissue ischemia limits the maximum safely applied tension far more than the risk

of mechanical damage such as bowel perforation, mesenteric tearing, and/or bowel tearing. Using laser Doppler perfusion imaging technology, the onset of ischemia was observed for applied tensile loads exceeding 90 gf.

This result guided the experimental procedures of the *in vivo* experiments using the Instrumented SMA Driven Ratchet by providing an upper bound of the applied tensile load and has been critical for preventing complications with the porcine animal models. By following the procedure developed for porcine animal models, the tensile load associated with the onset of ischemia can be extended to human patients and used to guide enterogenesis device design, refine treatment on a patient-to-patient basis, and most importantly, prevent the complications related to applying excessive small bowel tension in a clinical setting.

6.6.2. Tissue Attachment

Although originally considered trivial ("just use sutures"), the challenge of reliably and safely transferring load from the enterogenesis device to the bowel wall persisted throughout this research. In addition to describing the successful Dilating Fenestrated Mesh approach, this section will discuss the important reasons why the unsuccessful attachment approaches were unreliable and/or unsafe.

6.6.2.1. Dilating Fenestrated Mesh

Reliably and safely attaching to the wall of the small bowel has been a constant challenge throughout this research. In a series of experimental studies evaluating a range of tissue attachment approaches, the Dilating Fenestrated Mesh concept has demonstrated robust attachment performance *and* the ability to operate in a detached state to facilitate implantation, removal, and purposeful repositioning of the attachment.

The biggest clinical implications of this attachment approach is the enablement of Natural Orifice Transluminal Endoscopic Surgery (NOTES) and other minimally invasive surgical techniques. With the attachments in their detached state, it will be possible to place an enterogenesis device into the remnant small bowel through the upper GI tract or through an ostomy without requiring any surgical manipulation of the small bowel. These surgical approaches can greatly improve the acceptance of the mechanotransductive treatment approach, eliminate the risk

of many surgical complications, prevent the development of intraperitoneal adhesions, prevent the creation of scars, and reduce the cost of treatment.

Additionally, the attachment approach is a significant contribution because its use can be extended to a number of other medical applications such as improving endoscopic maneuverability, anchoring an instrument within large blood vessels to accurately place stents or perform endovascular coiling, and applying tensile load to the esophagus for the treatment of long-gap esophageal atresia.

6.6.2.2. Unreliable and/or Unsafe Tissue Attachment Approaches

Very few attachment approaches in the intraluminal attachment study were considered both safe to use and able to transfer load without slipping. The shortcomings of the permanent (not designed to actively attach and detach) approaches and non-permanent (designed to actively attach and detach) approaches are described below.

6.6.2.2.1. Ill-Suited Permanent Attachment Approaches

Although the goal of the attachment study (Chapter 4) was to develop a safe tissue attachment approach with the ability to operate in attached and detached states, several permanent attachment approaches were considered in the study. Permanent approaches included sutures (with and without reinforcement), surgically enforced binding/kinking, and tissue clamping. The surgically enforced tissue binding/kinking approach was not effective because the enterogenesis device was able to slide despite the bends in the bowel. Even if effective, this approach is prone to creating diverticulum (pouches of bowel tissue growth not-aligned with the bowel). The tissue clamping and suture approaches were not reliable because of adaptations undergone by the bowel during the distraction period. For both approaches, the attachments displayed a tendency to slip through the full thickness of the bowel tissue, rendering the attachments completely ineffective during latter portions of the distraction period.

6.6.2.2.2. Ill-Suited Non-Permanent Attachment Approaches

Attachment approaches with the ability to apply high loads without slipping, such as impingement and suction approaches, were also considered the most likely to cause bowel ischemia and subsequent perforation. The dilation approach using smooth balloons was considered the safest approach, but unless the balloons were inflated enough to cause acute ischemia, they

easily slid along the bowel lumen at low loads. Texturing balloons with an abrasive mesh made it possible to attach without causing acute ischemia. However, the detachment performance of these attachments was so poor that it was nearly impossible to implant and remove the prototypes during acute *in vivo* experiments. This challenge led to the development of the Fenestrated Dilating Mesh approach, which demonstrated strong attachment and detachment performance without risking tissue ischemia and subsequent perforation.

6.6.3. Device Form

Many of the findings of this dissertation relate to the importance of the device form. The considerations for and relationships between length, rigidity, curvature, diameter, tissue interfaces, the local feature contours are important to understand in order to design enterogenesis devices that are safe to implant, operate, and remove. The findings here were developed over the course of this dissertation through many experiences in the operating room with porcine animal models.

6.6.3.1. Length, Rigidity and Curvature

The length, rigidity, and curvature of an enterogenesis device are coupled parameters in the context of device maneuverability through the GI tract, the fit of the device within the peritoneal cavity, and the stress the implanted device places on the mesentery. For example, if the device length is very short, it may still be implantable through the upper GI tract even if it is rigid and straight. Likewise, long devices must have some flexibility to be maneuvered through the upper GI tract. The maximum length of a device, regardless of implantation and removal procedure, is also limited by the size of the patient's peritoneal cavity and by the extent that the device induces stress in the mesentery supporting the bowel. Because the mesentery radially pulls on the bowel, giving the bowel curvature, long and straight devices place significant stress on the mesentery. To reduce mesenteric stress, long devices can be curved to mimic the natural curvature of the bowel, as was done with the Curved Hydraulic Device, or shortened like the Reciprocating Linear Hydraulic Device.

6.6.3.2. Diameter

In general, the outer diameter of an enterogenesis device must be limited such that the device fits within the diameter of the relaxed bowel lumen. However, a more restrictive requirement exists for enterogenesis devices designed to be implanted in continuous bowel because the flow of enteral

contents must not be obstructed by the device. To eliminate the risk of device-related bowel obstruction, which can lead to bacterial overgrowth and a cascade of further medical complications, both the device length and outer diameter should be decreased in order to reduce the resistance of enteral content flow.

6.6.3.3. Proximal and Distal Bowel Tissue Interface

The proximal and distal bowel tissue interface an of enterogenesis device needs to be carefully designed to reduce the potential risk of bowel ischemia on either end of the device. This is because the manner in which the tissue drapes around the device can lead to sharp bends in the tissue that lead to ischemia and perforation. Methods to prevent this include designing flexibility and or curvature into the devices. For rigid devices, tissue guides can be incorporated that transition from the rigidity of the device to the compliance of the tissue.

6.6.3.4. Local Feature Contours

Local enterogenesis device features that interface with the bowel lumen must be contoured such that they do not induce bowel ischemia. The ischemia risk of uncontoured features is coupled to the device outer diameter, because as the outer diameter increases, the features on the device must become more contoured to prevent bowel ischemia. This consideration is particularly pertinent at the tissue attachment locations of the device, which often have the greatest outer diameter.

6.7. Impact

This dissertation has laid the complete engineering and medical foundation for the design and usage of enterogenesis devices for correcting short bowel syndrome. The medical foundation was set by the establishment of the treatment feasibility, and strengthened by identifying the maximum safely applied tensile load and evaluating the effect of different load and displacement-based tissue expansion strategies. In addition, the demonstrated medical viability of the payout approach has huge ramifications on the design of enterogenesis devices, enabling their compact design by breaking the tradeoff between device size and tissue expansion capability. The engineering foundation was set by the development of specifications for clinical device design, the design of and validation of three unique expansion architectures, the force instrumentation system, and the Dilating Fenestrated Mesh attachment approach. This foundation will guide the refinement of the

Reciprocating Linear Hydraulic Device designed in Chapter 5, eventually leading to clinical studies with the potential to provide an essential and life-saving alternative treatment approach for patients with short bowel syndrome.

The focus of this dissertation was on the mechanotransductive correction of short bowel syndrome, but the impact is far-reaching. The most direct extension of the engineering foundation provided by this dissertation regards the treatment of long-gap esophageal atresia (LGEA), a serious condition where a large portion of the patient's esophagus is missing at birth. While the mechanotransductive treatment of this condition has already been achieved by the application of distractive forces on the esophagus (known as the Foker method [7,2,8]), the transfer of load to the esophagus is currently achieved with sutures manually tensioned from outside the patient. As with porcine small bowel in this research, the sutures tend to slip through the esophagus of these patients, requiring additional thoracotomies to replace them and continue treatment. This is potentially an ideal application of the Dilating Fenestrated Mesh attachment approach, because the requirements for attachment, detachment, and safety overlap significantly. Additionally, the force instrumentation system developed in Chapter Three could be extended for treating LGEA to give medical personal a real-time measurement of the esophageal tension, allowing them to avoid the application of injurious loads and/or maintain the consistent application of tension. The Dilating Fenestrated Mesh could also be extended to other medical applications. To provide improved endoscope maneuverability, the Dilating Fenestrated Mesh could replace the smooth balloons used in double-balloon endoscopy procedures; the approach could be used for anchoring instruments within large blood vessels to accurately place stents or perform endovascular coiling; and the approach could also be potentially used to perform mucosal biopsy of the GI tract.

6.8. Future Research

The future direction of this research should address important surgical and engineering challenges related to researching mechanotransductive enterogenesis, which include further developing the clinical approach and refining the design of the Reciprocating Linear Hydraulic Device.

6.8.1. Medical and Surgical Challenges

The current main challenges to conducting mechanotransduction-based enterogenesis studies is the formation of intraperitoneal adhesions following the implantation surgery, and the accurate measurement of the macroscopic net bowel growth with non-permanent attachments.

6.8.1.1. Improving the Measurement of Small Bowel Growth

The method used to measure net bowel growth in the *in vivo* experiments of this dissertation has been to place marking sutures in the Roux limb during the implantation surgery, measure the distance between adjacent sutures with a ruler, and remeasure the distance between adjacent sutures at the explant surgery for comparison. This method is complicated by two issues. First, bowel tissue exhibits high elongation for small changes in the applied tension, so manipulating the tissue in order to physically take the length measurement between sutures is prone to error. To mitigate this source of error, measurements were made with the bowel resting in the surgical field where possible. The second and more important problem related to this approach to measurement is that the marking sutures tend to slip out of the tissue, particularly for experiments exceeding one week. In experiments where the number of counted marking sutures does not change between the implant and explant surgeries, measurements of net bowel lengthening were made with confidence. However, such experiments were not the norm. When a mismatch in the number of marking sutures is discovered at explant, it can be difficult if not impossible to make conclusive statements about the net lengthening of the bowel tissue. For example, in the *in vivo* experiment to demonstrate the viability of the Payout Approach with the Reciprocating Linear Hydraulic Device, it was not possible to conclude whether the tissue grew by 120% or 200% of the device stroke. In the short term, the problem of the sutures slipping through the tissue may be solved by:

1. exploring the reliability of different thread diameter and suturing materials (silk, prolene, nylon, polyester, etc.),
2. placing multiple (redundant) sutures circumferentially around the tissue, and
3. alternating suture colors in a pattern to identify which sutures have slipped at explant.

A more fundamental issue with the current approach to measuring small bowel growth is that placing the marking sutures is an invasive open-cavity procedure. When the ability to implant an enterogenesis device with minimally invasive surgical techniques is achieved, an alternative

measurement approach will be required. One possibility is that the device could be modified to place radiopaque (for radiographs) or high density (for fluoroscopy) tissue markers during the implant. However, they too would be likely to slip through the bowel thickness and become unrecoverable for experiments exceeding one week.

6.8.1.2. Addressing the Formation of Adhesions

Post-surgical tissue adhesions form in the peritoneum, connecting loops of bowel to adjacent loops, the peritoneum, and to organs such as the liver and spleen. At explant surgeries, the adhesions must be carefully broken down to locate the Roux limb and implanted device. In severe cases, removing adhesions can require damaging tissue, which can make it difficult to determine if damaged tissue is the result of the enterogenesis device or from the separation of adhesed tissues. Furthermore, during the distraction period, adhesions on the growth segment with neighboring tissues can create non-optimal load paths away from the growth segment. Thus, the load applied by the enterogenesis device to the growth segment may be significantly less than expected or measured. In a clinical setting, adhesions can lead to serious consequences such as chronic pain, bowel obstruction, bowel necrosis, and others. To address the formation of adhesions for both research and clinical applications, the use of adhesion preventing film, delaying the distraction period, and minimally invasive surgical techniques are discussed.

6.8.1.2.1. Adhesion Preventing Film and Gels

The use of an adhesion preventing film (Seprafilm®) may reduce adhesions and has been tried in a number of the *in vivo* experiments of this dissertation, but there were no significant changes in the adhesions encountered during the explants. Additionally, Seprafilm® and other adhesion preventing films and gels may prevent tissue healing and should thus be placed very carefully. Nonetheless, adhesion preventing films and gels should be considered in clinical trials if adhesions are an issue, despite their insignificant impact during the *in vivo* experiments of this dissertation.

6.8.1.2.2. Delaying the Distraction Period

In porcine models, adhesions begin to form in the days following the implantation surgery, worsen (strengthen) for two to three weeks, and then begin to dissipate naturally. Thus, delaying the distraction period following the creation of the Roux limb may be a method to prevent adhesions from creating non-optimal loading paths away from the growth segment. Additionally,

locating the growth segment would be much easier at explant, because less effort would be required to separate the adhesions. Disadvantages to this approach would be the increased cost of each experiment, because of the daily costs associated with housing and caring for the animals; the increased time to run each experiment; and difficulty using the current tissue measurement technique, because the marking sutures would not be recoverable at the explant.

6.8.1.2.3. Minimally Invasive Surgical Techniques

To prevent adhesions from forming in the first place, the use of device implantation techniques that do not expose the peritoneum to open air should be a goal. Challenges to this endeavor are strongly coupled to the size, curvature, rigidity, and attachment approaches used in current enterogenesis devices. Additionally, a non-invasive method for measuring net bowel lengthening would be required to validate the success of the enterogenesis device.

To place an enterogenesis device into the small bowel without surgically manipulating the tissue, the device could potentially be placed through the upper GI tract or through a preexisting gastrostomy/jejunostomy. In either scenario, the attachments of the enterogenesis device would need to operate in attached (to apply tensile loading) and detached (to implant/remove) states. Additionally, the enterogenesis device would need to be compact and potentially flexible to enable its placement through the upper GI tract.

6.8.2. Engineering Challenges

Future engineering research will focus on enterogenesis device improvements that enable the Reciprocating Linear Hydraulic Device to be implanted in the continuous GI tract rather than in an isolated segment, enable the device to be implanted by non-invasive or less invasive surgical techniques, instrumenting the device, and automating its control.

6.8.2.1. Expansion Mechanism Improvements

The expansion mechanism of the Reciprocating Linear Hydraulic Device is composed primarily of stainless steel tubing, making the device rigid and straight. As a result, stress on the mesentery was observed during the implant because the bowel is naturally curved by the mesentery. By bending the housings to give the device a curvilinear form factor, the stress on the mesentery could be reduced. However, the device would still be rigid, and thus difficult or impossible to implant though the upper GI tract or through a preexisting gastrostomy/jejunostomy.

Thus, the development of a flexible expansion mechanism is critical to enabling minimally invasive surgical techniques. Ideally, the device could be placed through the upper GI tract and into the remnant bowel without leading to device-related bowel obstruction. To achieve this, enteral contents must be able to flow through or around the expansion mechanism and attachments.

6.8.2.1.1. Flexible Expansion Mechanism

Designing a reciprocating flexible expansion mechanism will greatly improve the surgical options for implanting and removing the enterogenesis device. To achieve this, many feasible architectures will be considered from the soft robotics community that can be scaled and modified for studying bowel growth in porcine models and correcting SBS in both infants and adults. Examples of applicable expansion mechanisms include pneumatic bellows [9], fiber-reinforced elastomeric enclosures [10], and miniature McKibben actuators [11]. To evaluate a range of flexible expansion mechanism quickly, recent advances in thermoplastic elastomers (TPEs) for additive manufacturing can be used to print flexible models. Once a flexible expansion mechanism architecture is downselected, more traditional manufacturing processes such as TPE injection molding can be used to fabricate functional and high quality prototypes.

6.8.2.1.2. Allowing Flow Through or Around the Device

In addition to developing an expansion mechanism that is flexible, the expansion mechanism must allow the flow of enteral contents either through a channel of the device or around the outside of the device to enable its implantation in the continuous GI tract. The benefit of implanting in the continuous GI tract is that non-invasive surgical techniques may be used. Furthermore, isolating a segment of the small bowel from the GI tract can lead to disuse atrophy, because the isolated segment is not exposed to enteral contents. For patients that are receiving fully parenteral nutrition, the requirement for the device to allow for flow-through is still relevant to allow the passage of proximally secreted fluids.

A pilot study of flow-through with simulated enteral contents (SEC), *ex vivo* segments of porcine bowel, and a small set of prototype attachments was conducted to correlate the percent area of small bowel blocked with the flow-through rate [12]. The study concluded that even with a 75% decrease in flow-through area, the rate of SEC was not significantly altered. Although this study was promising, it did not account for an overall resistance to flow, which would include both

the decrease in the cross-sectional area of flow and the length of bowel over which it acts. Additionally, conducting a flow-through study with a living animal model is important, because *ex vivo* studies cannot account for peristaltic action.

6.8.2.2. Instrumentation and Control

The current Reciprocating Linear Hydraulic Device is not instrumented to measure the applied bowel force or device expansion, nor is its control automated. Studies with the Instrumented SMA Driven Ratchet demonstrated the value of measuring the applied load. Force instrumentation made it possible to keep the applied tensile load within a safe range and also allowed the expansion of the tissue to proceed at unprecedented rates without affecting tissue health. For the Reciprocating Linear Hydraulic Device, measuring the applied tensile bowel force would increase the rate of small bowel growth by informing the timing of the payout approach operation. In the *in vivo* study using the Reciprocating Linear Hydraulic Device, four hours were given for the bowel to respond to the applied tensile load before resetting the device and repeating the operation. The four hour time span may have been too long, resulting in slower than necessary growth, or too short, resulting in the bowel not growing sufficiently between payout operation cycles. Ideally, with force instrumentation, the time given for the bowel to grow could be based on when the measured load reaches a low force threshold, which may vary greatly from cycle to cycle and from animal model to animal model. To provide this flexibility, automating the control of the hydraulic line that drives the device expansion and the pneumatic lines that drive the inflation of the attachments is key, especially if the cycle period is short. To design the data acquisition and control system of the Reciprocating Linear Hydraulic Device for porcine animal models, it will be critical to miniaturize the pumps, electronics, and power sources, because porcine animal models do not tolerate large and/or heavy devices on their back. For clinical applications, external equipment will not be an issue.

6.9. Closing

Prior to this research, little was known about how to develop the load-based approach to growing small bowel tissue for correcting short bowel syndrome, both in a surgical and in an engineering context, although numerous promising studies with small animal models hinted at the clinical feasibility of the approach. This dissertation has transitioned the technological state of the

art for enterogenesis devices tremendously through the development of novel enterogenesis devices, actuation architectures, the force instrumentation system, and tissue attachment approaches. These technological advances have enabled medical studies establishing the clinical feasibility of the treatment method, set guidelines for the safe application of load on bowel tissue, provided insight on how to effectively expand small bowel tissue to induce growth rapidly, and demonstrated the viability of the advantageous payout approach for inducing small bowel growth.

Although much progress has been made, a continued research effort to refine enterogenesis device technologies and medical research techniques will be needed to achieve the ultimate goal of saving the lives of SBS patients by inducing the growth of their remnant bowel. From an engineering perspective, the future work will focus on providing a compact, instrumented, and flexible expansion mechanism that allows enteral content flow through, thus enabling the placement of an enterogenesis device into the non-isolated remnant bowel segment by non-invasive surgical techniques. Future surgical and medical research will focus on accurately measuring the growth of small bowel, addressing the problem of intraperitoneal adhesion formation, and developing minimally invasive surgical device implantation and removal techniques. There is great confidence that the interdisciplinary team of engineers and surgeons conducting this research will overcome these difficult challenges, as we have done successfully in the past, and make the mechanotransductive approach to correcting short bowel syndrome a clinical reality, improving the quality of care for those afflicted with short bowel syndrome and ultimately saving lives.

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